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(21) International Application Number: PCT/US96/20746 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 60/009,185 22 December 1995 (22.12.95) US (71) Applicants (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plain, NJ 07950 (US). COCENSYS, INC. [US/US]; 213 Technology Drive, Irvine, CA 92618 (US).	(71)(72) Applicants and Inventors: BIGGE, Christopher, F. [US/US]; Apartment #6, 1856 Stadium Place, Ann Arbor, MI 48103 (US). CAI, Sui Xiong [CN/US]; 12 Salinas, Foothill Ranch, CA 92610 (US). KEANA, John, F., W. [US/US]; 3854 Onyx Street, Eugene, OR 97405 (US). LAN, Nancy, C. [US/US]; 522 Hermosa Street, South Pasadena, CA 91030 (US). GUZIKOWSKI, Anthony, P. [US/US]; 2647 Quince Street, Eugene, OR 97404 (US). ZHOU, Zhang-Lin [CN/US]; 15 Bearpaw #12-A, Irvine, CA 92604 (US). ARALDI, Gian, Luca [IT/US]; 3609 38th Street N.W., #403, Washington, DC 20016 (US). LAMUNYON, Donald [US/US]; 590 Halton Lane #22, Junction City, OR 97448 (US). WEBER, Eckard [US/US]; 1290 Morningside, Laguna Beach, CA 92651 (US). (74) Agents: MANDRA, Raymond, R.; Fitzpatrick, Cella, Harper & Scinto, 277 Park Avenue, New York, NY 10172 (US) et al. (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: SUBTYPE-SELECTIVE NMDA RECEPTOR LIGANDS AND THE USE THEREOF (57) Abstract The invention relates to subtype-selective NMDA receptor ligands and the use thereof for treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, psychosis, convulsions, aminoglycoside antibiotics-induced hearing loss, migraine headache, chronic pain, Parkinson's disease, glaucoma, CMV retinitis, urinary incontinence, opioid tolerance or withdrawal, and inducing anesthesia, as well as for enhancing cognition.		

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TITLE

Subtype-Selective NMDA Receptor Ligands
and the Use Thereof

BACKGROUND OF THE INVENTION

Field of the Invention

5 This invention is related to 2-substituted piperidine
analogs. The analogs are selectively active as
antagonists of N-methyl-D-aspartate (NMDA) receptor
subtypes. The invention is also directed to the use of
2-substituted piperidine analogs as neuroprotective
10 agents for treating conditions such as stroke, cerebral
ischemia, central nervous system trauma, hypoglycemia,
anxiety, convulsions, aminoglycoside antibiotics-
induced hearing loss, migraine headaches, chronic pain,
glaucoma, CMV retinitis, psychosis, urinary
15 incontinence, opioid tolerance or withdrawal, or neuro-
degenerative disorders such as lathyrism, Alzheimer's
Disease, Parkinsonism and Huntington's Disease.

Related Background Art

20

Excessive excitation by neurotransmitters can cause the
degeneration and death of neurons. It is believed that
this degeneration is in part mediated by the
excitotoxic actions of the excitatory amino acids (EAA)

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glutamate and aspartate at the N-methyl-D-Aspartate (NMDA) receptor. This excitotoxic action is considered responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery and cerebral trauma, as well as lathyrism, Alzheimer's Disease, Parkinson's Disease and Huntington's Disease.

Excitatory amino acid receptor antagonists that block NMDA receptors are recognized for usefulness in the treatment of disorders. NMDA receptors are intimately involved in the phenomenon of excitotoxicity, which may be a critical determinant of outcome of several neurological disorders. Disorders known to be responsive to blockade of the NMDA receptor include acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, neuropathic pain and anxiety, and may be a significant causal factor in chronic neurodegenerative disorders such as Parkinson's disease [T. Klockgether, L. Turski, Ann. Neurol. 34, 585-593 (1993)], human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis (ALS), Alzheimer's disease [P.T. Francis, N.R. Sims, A.W. Procter, D.M. Bowen, J. Neurochem. 60 (5), 1589-1604 (1993)] and Huntington's disease. [See S. Lipton, TINS 16 (12), 527-532 (1993); S.A. Lipton, P.A. Rosenberg, New Eng. J. Med. 330 (9), 613-622 (1994); and C.F. Bigge, Biochem. Pharmacol. 45, 1547-1561 (1993) and references cited therein.]. NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control withdrawal symptoms from addictive drugs (Eur. Pat. Appl. 488,959A).

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U.S. Patent 5,352,683, discloses the treatment of chronic pain with a compound which is an antagonist of the NMDA receptor.

5 U.S. Patent 4,902,695, discloses certain competitive NMDA antagonists that are useful for the treatment of neurological disorders, including epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, and neurodegenerative diseases such as Alzheimer's disease
10 and Huntington's disease.

U.S. Patent 5,192,751 discloses a method of treating urinary incontinence in a mammal which comprises administering an effective amount of a competitive NMDA
15 antagonist.

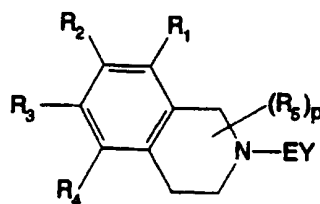
Evidence indicates that the NMDA receptor comprises a class of such receptors with different subunits. Molecular cloning has revealed the existence of at
20 least five subunits of the NMDA receptors designated NR1 & NR2A through 2D. It has been demonstrated that the co-expression of NR1 with one of the NR2 subunits forms a receptor with a functional ion channel. (*Ann. Rev. Neurosci.* 17:31-108(1994)). It is thought that
25 NMDA receptors with different subunit composition generate the different NMDA receptor subtypes found in the mammalian brain.

An object of this invention is to provide novel -
30 subtype-selective NMDA receptor ligands.

SUMMARY OF THE INVENTION

The invention relates to a subtype-selective NMDA
35 receptor ligand having the Formula (I):

- 4 -



5 wherein

R₁-R₄ are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, cyanamido, N(CN)₂, guanidino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

15 E is (CR_aR_b)_r-G_s-(CR_cR_d)_t, wherein R_a, R_b, R_c and R_d are independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy or carboxy; G is oxygen, sulfur, sulfone, sulfoxide, carboxy (CO₂ or O₂C), carbonyl (CO), or NR_e, wherein R_e is hydrogen, alkyl or aryl; r and t are independently 0, 1, 2, 3, 4, or 5; and s is 0 or 1;

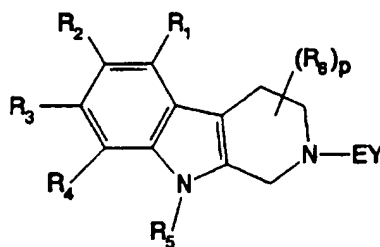
25 R_s is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

30 p is 0, 1, 2, or 3;

Y is hydrogen, hydroxy, CH₃, CN, CO₂R, sulfate, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally

- 5 -

- substituted aroyl, $\Rightarrow Y_1$, $\Rightarrow Y_1$ (which may be cis or trans, throughout) carbonylamido, hydrazino, oximo, amidino, optionally substituted heterocyclic group, optionally substituted heterocycloxy, optionally substituted
- 5 heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted cycloalkoxy group, amino, amido, ureido, or guanidino; and
- 10 Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, optionally substituted cycloalkyl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl.
- 15 The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (II):



20

wherein

R₁-R₄, E, Y and Y₁ are the same as described in formula I;

25

R₅ is hydrogen, lower alkyl, acyl or aryl;

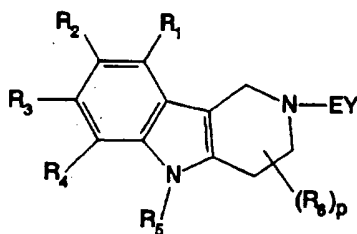
p is 0, 1, 2 or 3; and

- 30 R₆ is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a

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heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group; and

The invention also relates to a subtype-selective NMDA
5 receptor ligand having the Formula (IIa):



10 wherein

R₁-R₄, E, Y and Y₁ are the same as described in formula I;

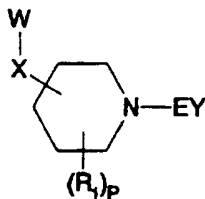
15 R₅ is hydrogen, lower alkyl, acyl or aryl;

p is 0, 1, 2 or 3; and

R₆ is hydrogen, hydroxy, alkylcarboxy, optionally
20 substituted aryl, optionally substituted aralkyl,
optionally substituted aryloxyalkyl, optionally
substituted benzyloxyalkyl, a heterocyclic group, a
heterocyclic substituted alkyl group, heteroaryl, or a
heteroaryl substituted alkyl group.

25

The invention also relates to a subtype-selective NMDA
receptor ligand having the Formula (III):



- 7 -

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

5

X is a bond, $(CH_2)_m$, carbonyl, oxygen, or NR;

E is the same as described in formula I;

10 Y is hydrogen, hydroxy, CH_3 , CN, CO_2R ; an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R is hydrogen, alkyl, aminoalkyl, amidoalkyl,
15 ureidoalkyl, or guanidinoalkyl;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a
20 heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

25

p is 0, 1, 2, 3 or 4.

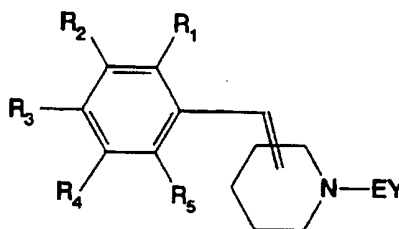
with the proviso, that when W is adamantyl or when p is greater than zero, or when the piperidine is
30 substituted in the 3-position by W-X, then Y may also be optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylthioxy, optionally substituted aroyl, $\equiv Y_1$, $\equiv Y_1$, optionally substituted heterocyclic group, optionally substituted
35 heterocycloxy, optionally substituted heteroaryl, optionally substituted heteroaryloxy, optionally substituted cycloalkyl group, optionally substituted

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cycloalkoxy group, amino, amido, ureido, or guanidino;
wherein

Y₁ is hydrogen, alkyl, hydroxyalkyl, optionally
5 substituted aralkyl, optionally substituted aryl,
optionally substituted cycloalkyl, aminoalkyl,
amidoalkyl, ureidoalkyl, or guanidinoalkyl.

The invention also relates to a subtype-selective NMDA
10 receptor ligand having the Formula (IV):



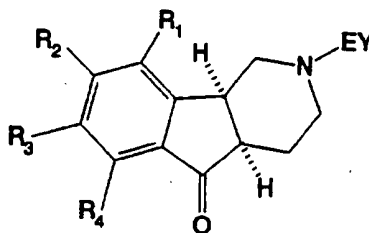
15 wherein

R₁-R₅ are independently hydrogen, halo, haloalkyl, aryl,
fused aryl, a heterocyclic group, a heteroaryl group,
alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl,
20 arylalkynyl, hydroxyalkyl, nitro, amino, cyano,
acylamido, hydroxy, thiol, acyloxy, azido, alkoxy,
carboxy, carbonylamido, or alkylthiol; and

E, Y and Y¹ are the same as described in formula I.

25

The invention also relates to a subtype-selective NMDA
receptor ligand having the Formula (V):



30

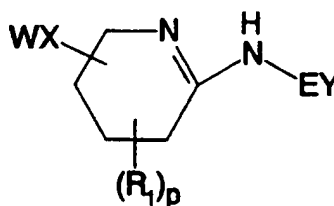
- 9 -

wherein

R_1 - R_4 , E, Y and Y_1 are the same as described in formula I.

5

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (VI):



10

wherein

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

15

X is a bond, $(CH_2)_m$, oxygen, or NR;

E, Y and Y_1 are the same as described in formula I;

20

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

25

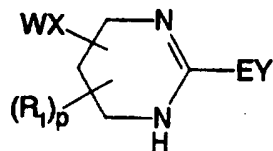
30

m is 0, 1, 2, or 3; and

q is 0, 1 or 2.

- 10 -

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (VII):



5

wherein

W is an adamantyl group, an optionally substituted aryl
10 group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

E, Y and Y_1 are the same as described in formula I;
15

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl
group, a ureidoalkyl group, or a guanidinoalkyl group;

R_1 is hydrogen, hydroxy, alkylcarboxy, optionally
20 substituted aryl, optionally substituted aralkyl,
optionally substituted aryloxyalkyl, optionally
substituted benzyloxyalkyl, a heterocyclic group, a
heterocyclic substituted alkyl group, heteroaryl, or a
heteroaryl substituted alkyl group;

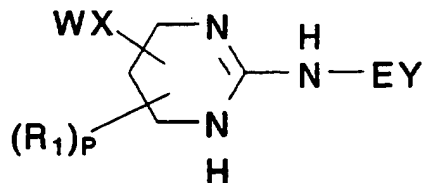
25

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

30 The invention also relates to a subtype-selective NMDA
receptor ligand having the Formula (VIII):

- 11 -



wherein

5

W is an adamantyl group, an optionally substituted aryl group, or an optionally substituted heteroaryl group;

X is a bond, $(CH_2)_m$, oxygen, or NR;

10

E, Y and Y_1 are the same as described in formula I;

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

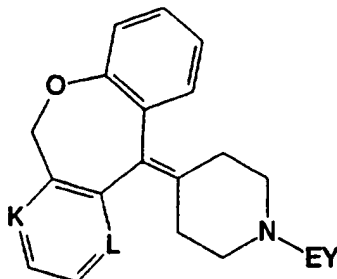
15 R_1 is hydrogen, hydroxy, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a
20 heteroaryl substituted alkyl group;

m is 0, 1, 2, or 3; and

p is 0, 1 or 2.

25

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (IX):



- 12 -

wherein

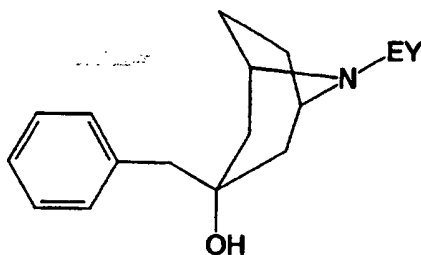
one of K and L is nitrogen and the other is CH; and

5

E, Y and Y₁ are the same as described in Formula I.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (X):

10



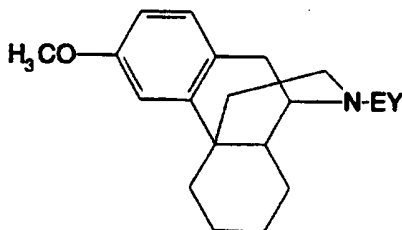
wherein

15

E, Y and Y₁ are the same as described in formula I.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (XI):

20



wherein

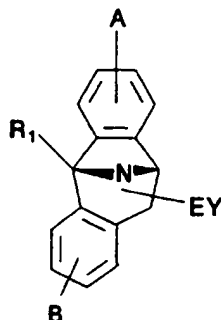
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E, Y and Y₁ are the same as described in formula 1.

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (XII):

30

- 13 -



wherein

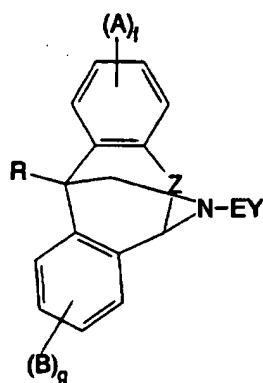
5

A and B are one or more substituents which are independently hydrogen, halo, alkoxy, trifluoromethylthio, cyano, carboxy or hydroxy;

10 R_1 is alkyl, alkenyl, aralkyl, cycloalkyl-alkyl, dialkylaminoalkyl, or hydroxyalkyl; and

E, Y and Y_1 are the same as described in formula I.

15 The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (XIII):



20

wherein

R is hydrogen, C_2 - C_6 acyl, C_1 - C_6 alkyl, aryl, C_1 - C_6 alkoxy carbonyl, C_7 - C_{10} aralkyl, C_2 - C_6 alkenyl, C_3 - C_{15}

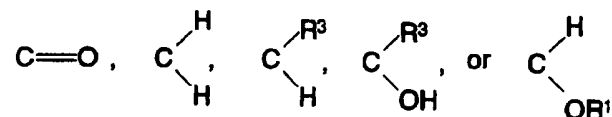
25 dialkylaminoalkyl, C_1 - C_6 hydroxyalkyl, C_2 - C_6 alkynyl, C_3 -

- 14 -

C₁₅ trialkylsilyl, C₄-C₁₀ alkylcycloalkyl, or C₃-C₆ cycloalkyl;

A and B are independently selected from the group
 5 consisting of a halogen such as chloro, fluoro, bromo, iodo, trifluoromethyl, azido, C₁-C₆ alkoxy, C₂-C₆ dialkoxymethyl, C₁-C₆ alkyl, cyano, C₃-C₁₅ dialkylaminoalkyl, carboxy, carboxamido, C₁-C₆ haloalkyl, C₁-C₆ haloalkylthio, allyl, aralkyl, C₃-C₆
 10 cycloalkyl, aroyl, aralkoxy, C₂-C₆ acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C₅-C₆ heterocycloalkyl, C₁-C₆ alkylthio, C₁-C₆ alkylsulfonyl, C₁-C₆ haloalkylsulfonyl, C₁-C₆ alkylsulfinyl, C₁-C₆ haloalkylsulfinyl, arylthio, C₁-C₆ haloalkoxy,
 15 amino, C₁-C₆ alkylamino, C₂-C₁₅ dialkylamino, hydroxy, carbamoyl, C₁-C₆ N-alkylcarbamoyl, C₂-C₁₅ N,N-dialkylcarbamoyl, nitro and C₂-C₁₅ dialkylsulfamoyl;

Z represents a group selected from
 20



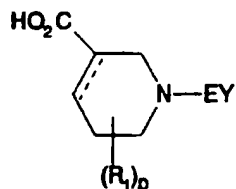
wherein R¹ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl,
 25 aralkyl, C₄-C₁₅ dialkylaminoalkyl, heterocycloalkyl, C₂-C₆ acyl, aroyl, or aralkanoyl, and R³ is C₁-C₆ alkyl, C₂-C₆ alkenyl, phenyl, aralkyl or C₃-C₁₅ dialkylaminoalkyl;
 and

30 f and g are independently integers selected from 0 (X or Y is hydrogen, respectively), 1, 2, 3, or 4; and

E, Y and Y₁ are the same as described in formal I.

- 15 -

The invention also relates to a subtype-selective NMDA receptor ligand having the Formula (XIV):



5

wherein

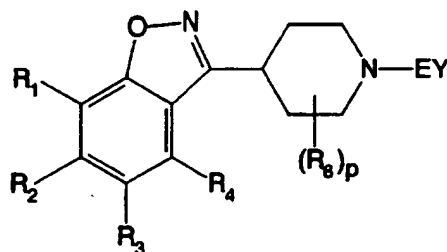
R_1 is carboxy or an alkylester or amide thereof; alkyl
10 carboxy or an alkyl ester or amide thereof; hydroxy or
hydroxymethyl group;

p is 0, 1 or 2;

15 the dotted line represents a single or double bond;

E , Y and Y_1 are the same as described in formula I.

The invention relates to a subtype-selective NMDA
20 receptor ligand having the Formula (XV):



25 wherein

R_1 - R_4 , E , Y and Y_1 are the same as described in formula
I;

30 R_6 is hydrogen, hydroxy, alkylcarboxy, optionally
substituted aryl, optionally substituted aralkyl,

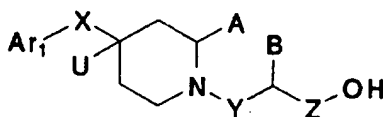
optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group; and

5

p is 0, 1, 2, or 3.

The invention relates to a subtype-selective NMDA receptor ligand having the Formula (XVI):

10



wherein Ar₁ is optionally substituted aryl or optionally substituted heteroaryl;

15

X is O, NR₁ or (CH₂)_n wherein n is 0, 1, 2, 3 or 4 and R₁ is hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

20

U is hydroxy or hydrogen;

Y is (CH₂)_m wherein m is 1, 2 or 3;

Z is (CHR₂)_z wherein z is 0, 1, 2, 3 or 4 and R₂ is hydroxy, hydrogen or a lower alkyl group having 1 to 6 carbon atoms; and

25

A and B are each hydrogen or together are (CH₂)_w wherein w is 0, 1, 2, 3 or 4.

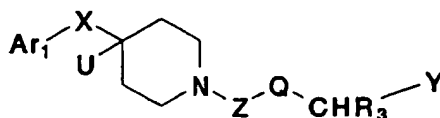
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Preferred substituents of Ar₁ include, for example, hydrogen, alkyl, a halogenated alkyl group such as a trifluoromethyl group, halogen, nitro, aryl, aralkyl, amino, a lower alkyl amino group or a lower alkoxy group.

35

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The invention relates to a subtype-selective NMDA receptor ligand having the Formula (XVII):



5

wherein

Ar₁ is optionally substituted aryl or optionally
10 substituted heteroaryl;

X is O, NR₁ or (CH₂)_n wherein n is 0, 1, 2, 3 or 4 and R₁ is hydrogen or a lower alkyl group having 1 to 6 carbon atoms;

15

U is hydroxy or hydrogen;

Z is (CHR₂)_z wherein z is 0, 1, 2, 3 or 4 and R₂ is hydroxy, hydrogen or a lower alkyl group having 1 to 6
20 carbon atoms;

Q is -CH=CH- or -C≡C-;

R₃ is hydrogen, hydroxy or hydroxy substituted lower
25 alkyl having 1 to 6 carbon atoms; and

Y is hydrogen, hydroxy, optionally substituted aryl or optionally substituted heteroaryl.

30 Preferred substituents of the aryl and heteroaryl groups include, for example, hydrogen, alkyl, a halogenated alkyl group such as a trifluoromethyl group, halogen, nitro, aryl, aralkyl, amino, a lower alkyl amino group or a lower alkoxy group.

35

- 18 -

The invention also relates to the quaternary ammonium salts of any one of the compounds above obtained by reacting the compound with a lower alkyl halide, preferable, methyl iodide or methyl sulfate.

5

The invention also relates to a method of treating or preventing neuronal loss associated with stroke, ischemia, CNS trauma, hypoglycemia and surgery, as well as treating neurodegenerative diseases including
10 Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease and Down's syndrome, treating or preventing the adverse consequences of the overstimulation of the excitatory amino acids, treating anxiety, psychosis, convulsions,
15 chronic pain, glaucoma, CMV retinitis, urinary incontinence, and inducing anesthesia, as well as enhancing cognition, and preventing opiate tolerance and withdrawal symptoms, comprising administering to an animal in need of such treatment an effective amount of
20 any one of the subtype-selective NMDA receptor ligands of the present invention, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

25

The present invention relates to the discovery of new compounds which are subtype-selective ligands of the NMDA receptor. There are a number of subtypes of the NMDA receptor including NR1A/2A, NR1A/2B, NR1A/2C and
30 NR1A/2D. The discovery of ligands which are selective for one or more of these subtypes allows for the treatment of various conditions mediated through binding to the NMDA receptor, while minimizing unwanted side effects.

35

Electrophysiological assays may be utilized to characterize the actions of potential subtype-selective

- 19 -

ligands at NMDA receptors expressed in *Xenopus* oocytes. The ligand may be assayed at the different subunit combinations of cloned rat NMDA receptors corresponding to the four putative NMDA receptor subtypes (Moriyoshi
5 et al., *Nature (Lond.)* 354:31-37 (1991); Monyer et al.,
Science (Washington, D.C.) 256:1217-1221 (1992);
Kutsuwada et al., *Nature (Lond.)* 358:36-41 (1992);
Sugihara et al., *Biochem. Biophys. Res. Comm.* 185:826-
832 (1992)).

10

Using fixed saturating concentrations of agonists (glutamate 100 μ M, glycine 1-10 μ M depending on subunit combination), the inhibitory potency of a putative
subtype-selective ligand may be assayed at the NMDA
15 receptors assembled from NR1A/2A, NR1A/2B, NR1A/2C and
NR1A/2D subunit combinations.

Preferably, the subtype selective NMDA receptor ligands are limited efficacy NMDA receptor antagonists. Such
20 limited efficacy antagonists are attractive because
such drugs have built-in safety margins; no matter how
high the dosage only a certain fraction of the response
can be blocked. This could be particularly important
for analgesic, anticonvulsant, anti-psychotic,
25 antimigraine headache, antiparkinson's disease and
antiglaucoma indications, where overdosage of full
antagonists may result in sedation. It is also likely
that limited efficacy NMDA receptor antagonists,
particularly those showing subtype-selectivity, will
30 not induce such profound memory deficits as full
antagonists.

Certain of the subtype-selective NMDA receptor ligands are expected to be able to mediate either inhibition or
35 potentiation of membrane current response. Which type
of effect predominates appears to be dependent upon the
subunit composition of the receptors and on the

- 20 -

- structure of the molecule. The 1A/2A and 1A/2B subtypes are mainly in the forebrain. The 1A/2C and 1A/2D are mainly in the cerebellum. In addition to the potential of developing subtype-selective drugs for the treatment of diseases associated with the overstimulation of the NMDA receptor with few side effects, it is also possible to develop drugs that selectively potentiate particular subtypes of NMDA receptors present in particular parts of the brain.
- Such drugs could show therapeutic potential as cognitive-enhancers in treatments of neurodegenerative conditions such as Alzheimer's disease. In addition, there is a potential for developing drugs that selectively potentiate some subtypes of NMDA receptors while simultaneously having inhibitory effects at other subtypes. Such compounds could be important for adjusting imbalances in subtype activity and may have therapeutic potential as psychotropic agents.
- Compounds that are useful for treating or preventing the adverse consequences of stroke, hypoglycemia, neurodegenerative disorders, anxiety, epilepsy or psychosis, or that induce analgesia, will inhibit the currents across the membranes of the oocyte expressing various subtype NMDA receptors. However, if the compound potentiates currents across the oocyte membrane, then the compound is expected to be useful in enhancing cognition.
- With respect to Formulae I-XVII, above:
- Typical C₆₋₁₄ aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.
- Typical halo groups include fluorine, chlorine, bromine and iodine.

Typical C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec.*-butyl, and *tert.*-butyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on any benzene ring of the compounds of the invention.

Typical C₂₋₄ alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec.*-butenyl.

10 Typical C₂₋₄ alkynyl groups include ethynyl, propynyl, butynyl, and 2-butyne groups.

Typical arylalkyl groups include any of the above-mentioned C₁₋₄ alkyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups.

Typical arylalkenyl groups include any of the above-mentioned C₂₋₄ alkenyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups.

20

Typical arylalkynyl groups include any of the above-mentioned C₂₋₄ alkynyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups.

25 Typical haloalkyl groups include C₁₋₄ alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

30

Typical hydroxyalkyl groups include C₁₋₄ alkyl groups substituted by hydroxy, e.g., hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

35 Typical alkoxy groups include oxygen substituted by one of the C₁₋₄ alkyl groups mentioned above.

Typical alkylthio groups include sulphur substituted by one of the C₁₋₄ alkyl groups mentioned above.

Typical acylamino groups include any C₁₋₆ acyl
5 (alkanoyl) substituted nitrogen, e.g., acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido as well as aryl-substituted C₂₋₆ substituted acyl groups.

10 Typical acyloxy groups include any C₁₋₆ acyloxy groups, e.g., acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

Typical heterocyclic groups include tetrahydrofuranyl,
15 pyranlyl, piperidinyl, piperizinyll, pyrrolidinyl, imidazolindinyl, imidazolinyll, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl and pyrazolinyl groups.

20 Typical heteroaryl groups include any one of the following which may be optionally substituted with one or more alkyl, halo, or hydroxy groups: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranlyl, isobenzofuranyl, chromenyl, xanthenyl,
25 phenoxathiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyll, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyll, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl,
30 quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl phenoxazinyl groups, 1,4-dihydroquinoxaline-2,3-dione, 7-amino
35 isocoumarin, pyrido[1,2-a]pyrimidin-4-one, 1,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxobenzimidazolyl, 2-oxindolyl and 4-nitrobenzofurazan.

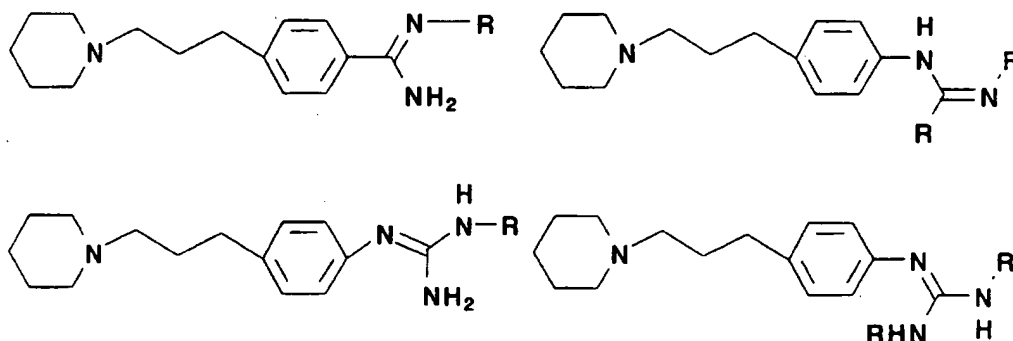
Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g., a pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide and the like.

5

Typical amino groups include -NH_2 , -NHR^{14} , and $\text{-NR}^{14}\text{R}^{15}$, wherein R^{14} and R^{15} are C_{1-4} alkyl groups as defined above.

- 10 Typical carbonylamido groups are carbonyl groups substituted by -NH_2 , -NHR^{14} , and $\text{-NR}^{14}\text{R}^{15}$ groups as defined above.

When the group is an amidino or guanidino group, any
15 one of the nitrogen atoms may be substituted, e.g.,



- 20 where each R is independently hydrogen, alkyl, or aryl.

Optional substituents on the aryl, aryloxy, arylthioxy, aroyl, heterocyclic, heterocycloxy, heteroaryl, heteroaryloxy, cycloalkyl, and cycloalkoxy groups
25 listed above include any one of the typical halo, haloalkyl, aryl, fused aryl, heterocyclic, heteroaryl, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy,
30 carboxy, carbonylamido, and alkylthiol groups mentioned above.

- In the compounds having the above formulae, the group E is a linker group between the nitrogen, e.g., piperidine nitrogen, and the terminal group Y. Excluded from such Formulae are where two heteroatoms are adjacent to one another such that an unstable compound would be produced. Such adjacent heteroatoms include -O-O-, -O-S- (divalent sulfur), -N-S- (divalent sulfur), -S-O- (divalent sulfur), and -S-N- (divalent sulfur). Hydrazine groups (-N-N-) are contemplated as possible linkers. Preferably, the group E is an optionally substituted methylene linker. Most preferably, the group E is a methylene linker $(CH_2)_n$, wherein n is 1, 2, 3, 4, 5 or 6.
- 15 Preferably, the group Y is an N-hydroxyalkylpiperidinyl (e.g., hydroxypropyl) group, which is expected to provide a reduction in affinity to the α_1 receptor, thereby resulting in less hypotension when the compounds are administered to animals. See, Gifford, R.W. et al., *Arch. Intern. Med.* 153:154-183 (1993). Alternatively, a halo group such as a p-chlorophenyl group may be employed to give compounds having a prolonged in vivo activity.
- 25 Compounds having Formula I may be prepared by reaction of an appropriately substituted 1,2,3,4-tetrahydroisoquinoline with a suitable electrophile in an aprotic solvent such as toluene or acetonitrile. The starting 1,2,3,4-tetrahydroisoquinoline may be prepared by the Pictet-Spenger method described in *Org. Reactions* 6:151-206 (1951). Optionally, a base such as potassium carbonate or pyridine may be added. Examples of suitable electrophiles include, for example, an alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, or heteroaralkyl halide, sulfate, sulfonate, or isocyanate. Specific examples of such electrophiles include ethyl 3-bromoethoxyphenyl acetate, methyl 5-

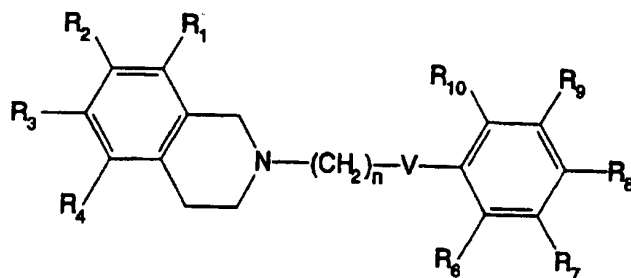
- 25 -

bromovalerate, ethyl 4-bromobutyrate, 3-butyne-1-methanesulfate, ethyl crotonate, 1-chloro-4-phenylbutane, 3-phenoxypropyl bromide, 4-chloro-4'-fluorobutyrophenone, 4-chlorobutyrophenone, 2-phenylethyl bromide, 1-bromo-3-phenylpropane, 3-phenoxypropyl bromide, β -bromo-phenetole, 3-phenoxypropyl bromide, 3-phenylpropyl bromide, 1,3-propanesulfone, phenylisocyanate, 4-nitrophenylisocyanate, allyl iodide, bromomethylcyclopropane, 3-bromo-1-propanol, and 5-bromovaleronitrile.

A general procedure for reaction of the piperidine-containing compound with an alkyl chloride, bromide, tosylate or mesylate involves forming a mixture of a free base of the amino derivative and an alkyl chloride or bromide in toluene, acetonitrile, DMF, acetone or ethanol, in the presence of NaI. The reaction may be refluxed for 1-10 h then cooled to room temperature, filtered and washed with hexane. The filtrate is evaporated, and the residue chromatographed over silica gel to give the product. If the product is a solid, it may be crystallized, for example, from hexane or hexane-ethyl acetate. If the product is an oil, it may be dissolved in acetone and 4N HCl solution in 1,4-dioxane or concentrated HCl may be added until the mixture becomes strongly acidic (pH < 2). It may then be rota-evaporated, and co-evaporated until a solid residue is obtained. The solid may then be recrystallized from acetone to give the hydrochloride.

Alternatively, the hydrobromide or other acid addition salts may be prepared by substitution of, for example, HBr or maleic acid for HCl.

Examples of compounds having Formula I include those having the Formula (Ia):



wherein

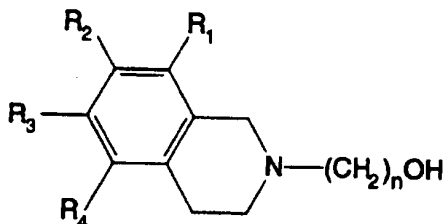
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R_1 - R_4 and R_6 - R_{10} are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

n is 1, 2, 3, or 4; and

15 V is CH_2 , oxygen, sulfur, or carbonyl (CO).

Other examples include those having the Formula (Ib):



20

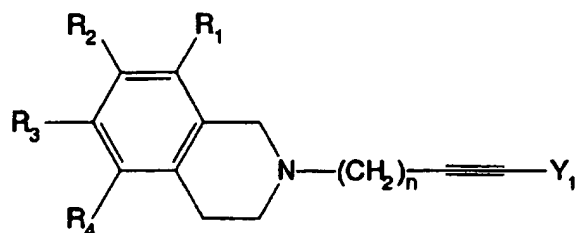
wherein

R_1 - R_4 are the same as described for formula Ia; and

25 n is 1, 2, 3, 4, 5, or 6.

Other examples include those having the Formula (Ic):

- 27 -



wherein

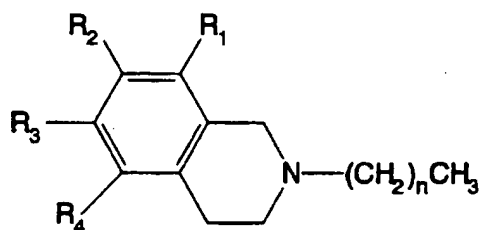
5

R_1 - R_4 are the same as described for formula Ia; and

Y_1 is alkyl, optionally substituted aryl, hydroxyalkyl, or optionally substituted alkaryl.

10

Other examples include those having the Formula (Id):



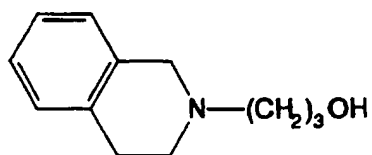
15 wherein

R_1 - R_4 are the same as described for formula Ia; and

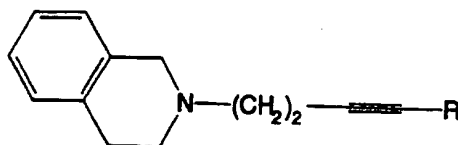
n is 1, 2, 3, 4, 5, or 6.

20

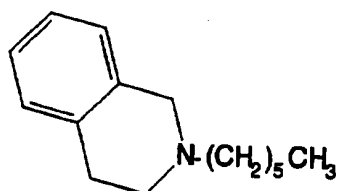
Particular examples of compounds having Formula I include



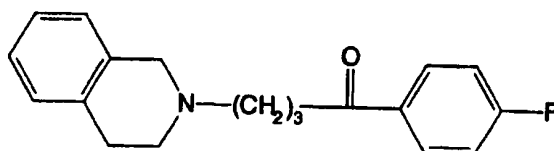
25



R = H, Ph;



5 and



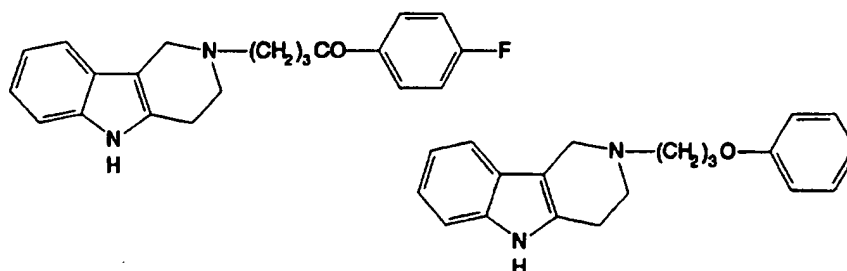
Compounds having Formula II may be prepared by reaction of an appropriately substituted 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole with an electrophilic reagent as mentioned above. The starting 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indoles may be prepared according to Abou-Gharbia et al., *J. Med. Chem.*, 30:1818-1823 (1987) and Habert et al., *J. Med. Chem.*, 23:635-643 (1980).

15

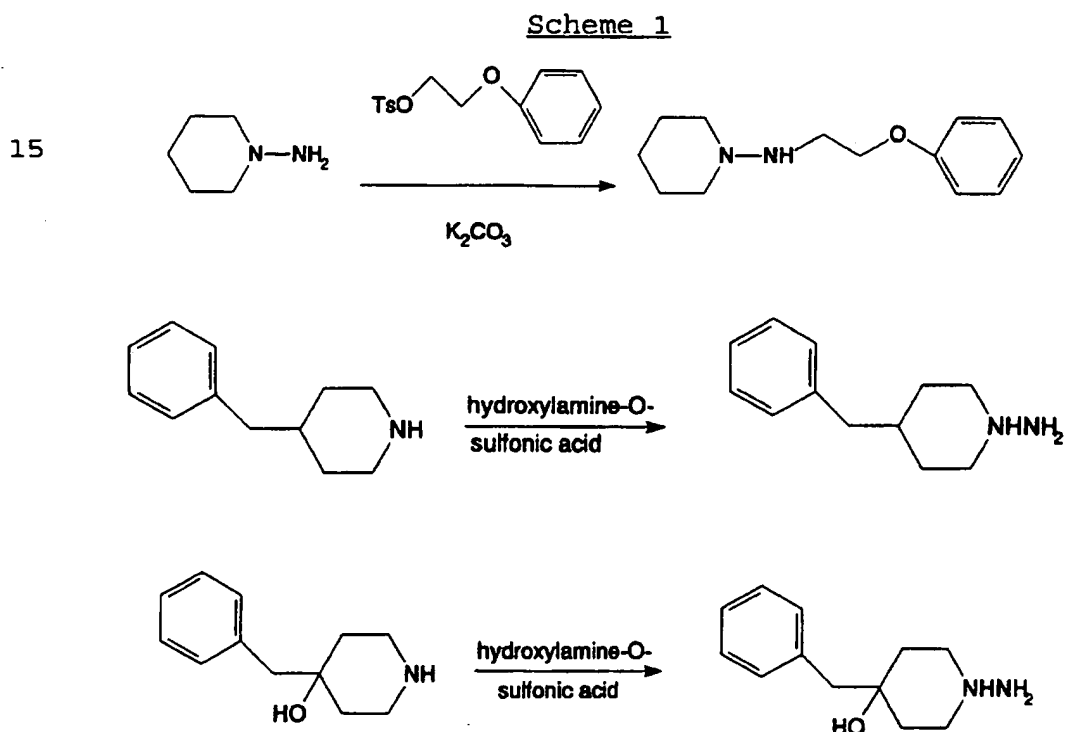
Particular examples of compounds having Formula II include 2-(2-phenoxyethyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole, 2-(3-phenoxypropyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole, 2-(3-phenylpropyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole and 2-(3-hydroxypropyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole.

Compounds having Formula IIa can be prepared similar to II. Particular examples of compounds having Formula IIa are

25



- With regard to Formula *III* when p is > 0 , then the
- 5 compounds may exist as a mixture of *cis* and *trans* isomers. The invention is directed to such *cis* and *trans* isomers as well as the individual enantiomers and diastereomeric mixtures.
- 10 When r is zero, G is NH and s is one, the *N*-amino piperidine compounds may be prepared according to Scheme 1:

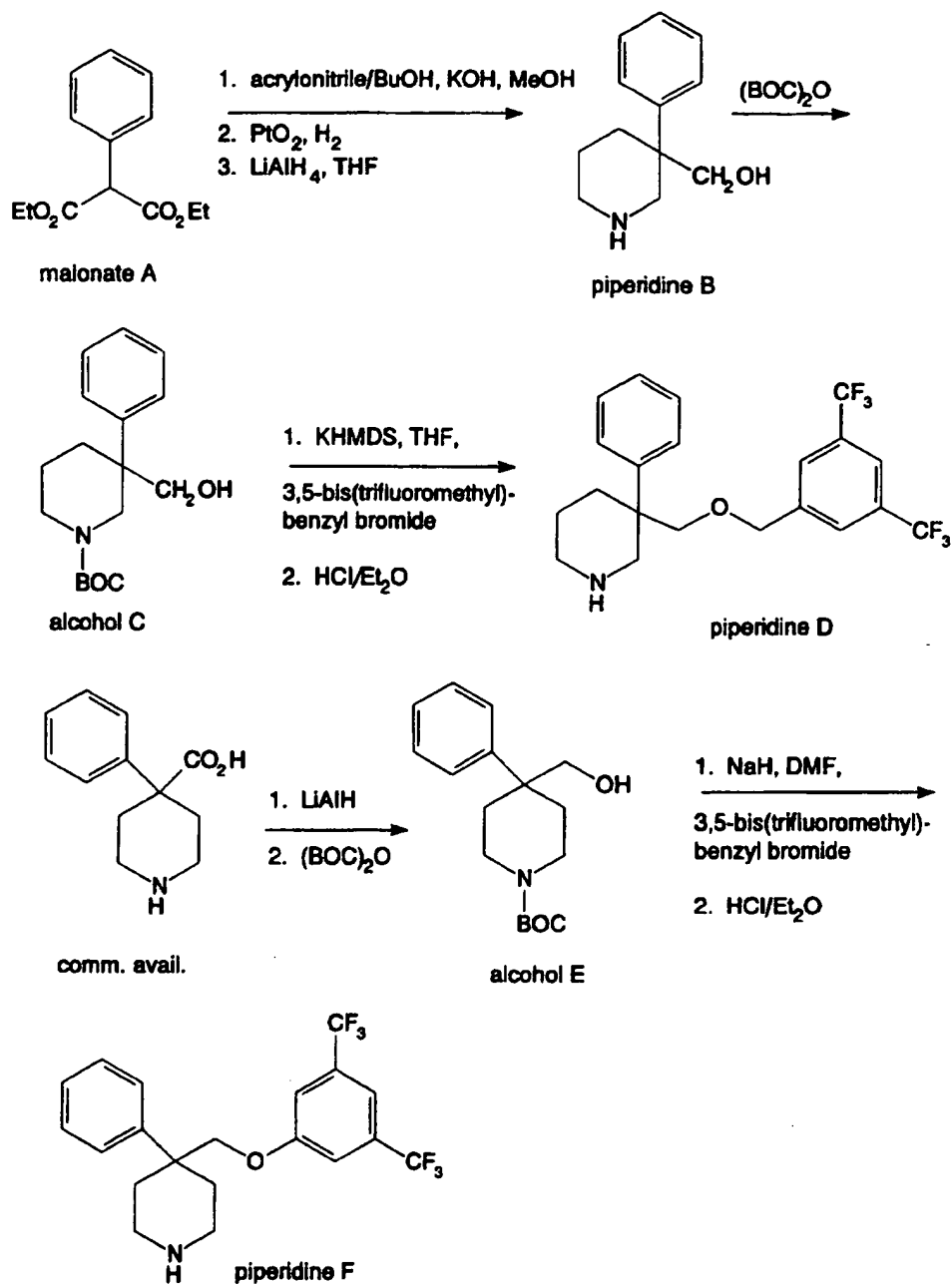


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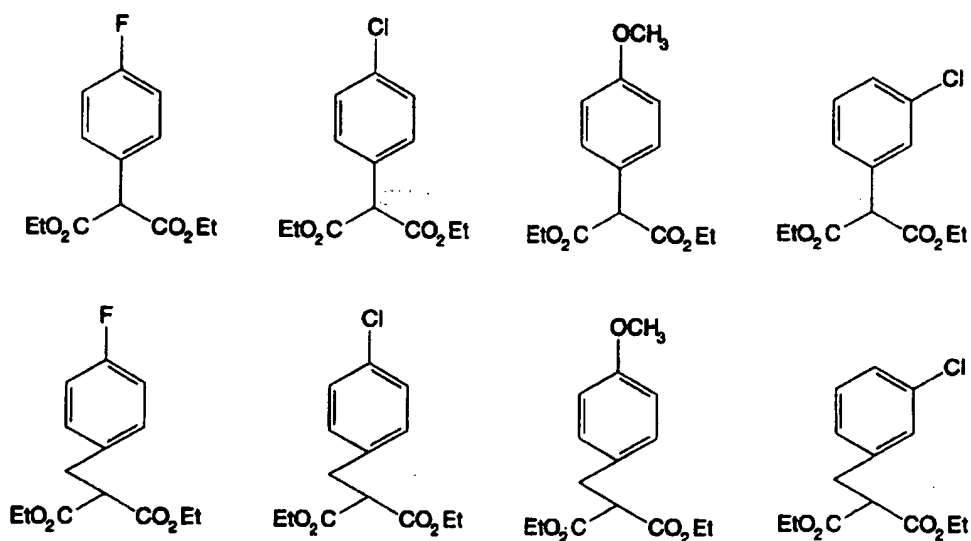
The N-amino piperidines may then be N-alkylated with one of the electrophiles listed above to give the compound of Formula **III**.

- 5 Also with regard to Formula **III**, when R₁ is an optionally substituted 2-aryloxyalkyl or an optionally substituted 2-benzyloxyalkyl-piperidine, the compounds may be prepared according to Scheme 2:

Scheme 2



Scheme 2 may be generalized so that malonate A might be any of a variety of aryl or substituted benzyl malonates, for example, those shown below, leading to the corresponding derivatives in the scheme. Each of those piperidines may be alkylated with one or the other of the electrophilic reagents mentioned above.



10 Scheme 3 depicts a route to some 2-substituted and 2,3-disubstituted-4-benzyl-4-hydroxypiperidines. A variety of electrophilic acylating agents may be used such that the final product 6 may have different

15 substituents on the nitrogen atom. Also note that a variety of Grignard reagents or other nucleophiles can be used in the step $2 \rightarrow 3$ so that the final product 6 may contain various substituents at the 2-position. Also note that a variety of alkylating agents can be

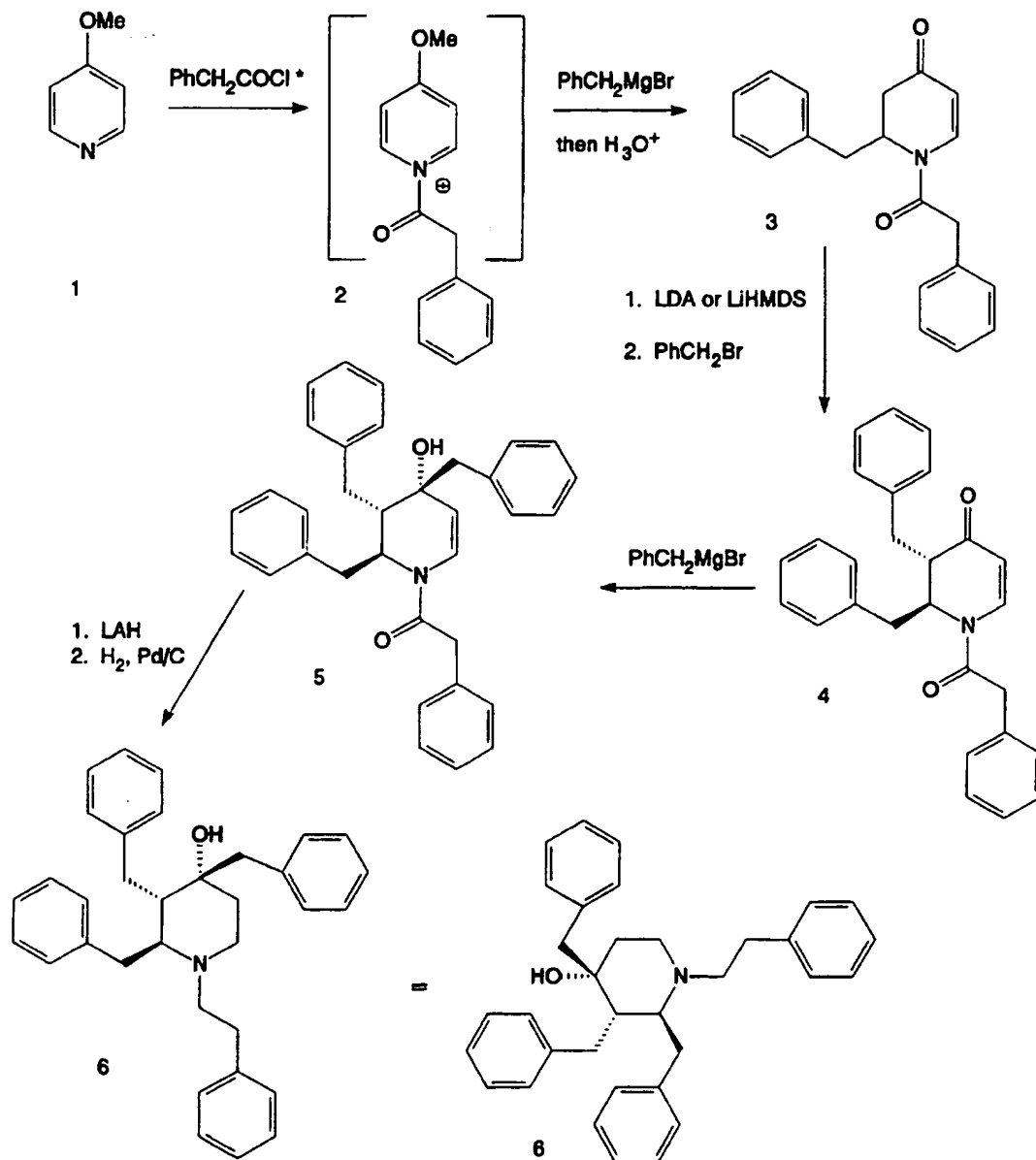
20 used in the step $3 \rightarrow 4$ so that the final product 6 will contain various substituents at the 3-position. Finally, the Grignard reagent in the step $4 \rightarrow 5$ can be used. Also note that a variety of Grignard reagents can be used so that the final product 6 will contain

25 various substituents at the 4-position. Alkylating agents may also include PhOCH_2Br and $\text{PhCH}_2\text{OCH}_2\text{Br}$, for

example. These would introduce oxygen atoms in the substituents at the various positions. Additionally, a high degree of stereocontrol can be achieved with the likely relative stereochemical outcomes shown.

5

Scheme 3

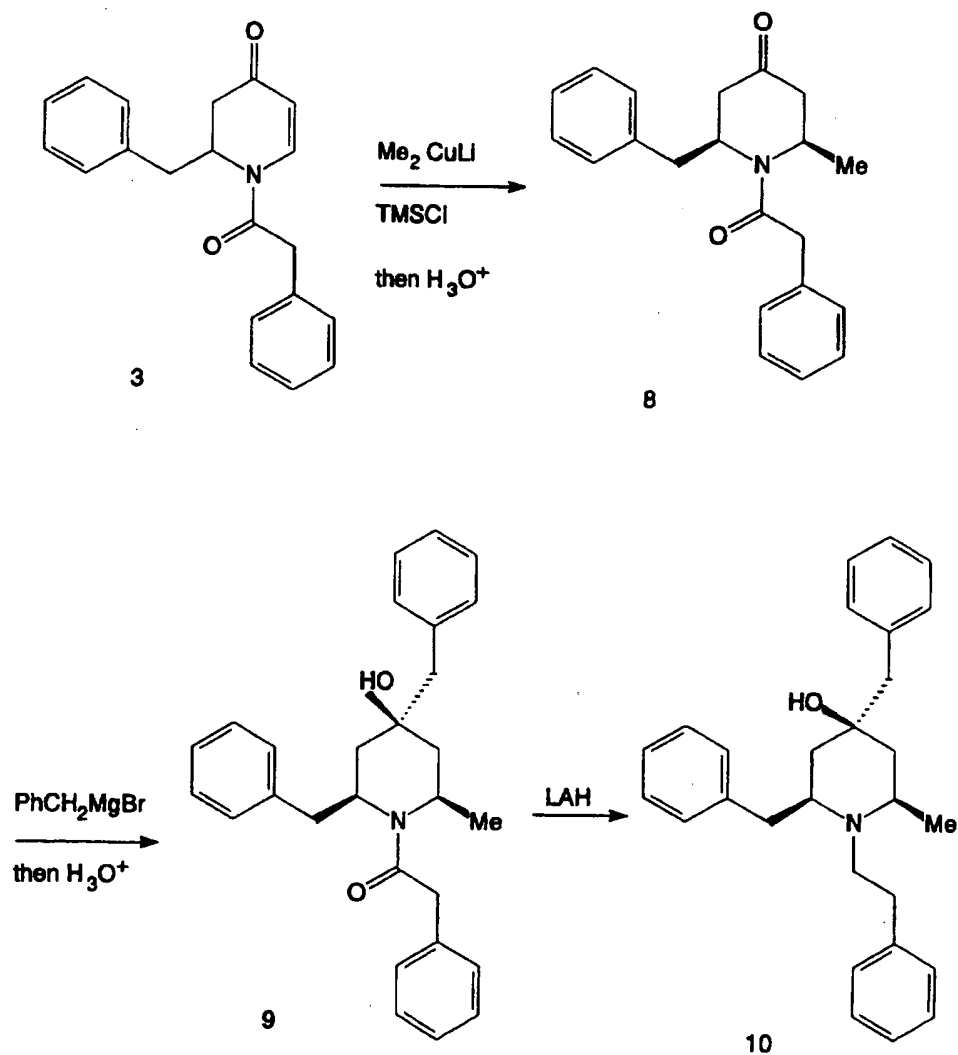


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*Other commercially available electrophilic acylating agents which may be used in the first step of Scheme 3 include $\text{Ph}(\text{CH}_2)_2\text{COCl}$ and $\text{PhOCH}_2\text{COCl}$.

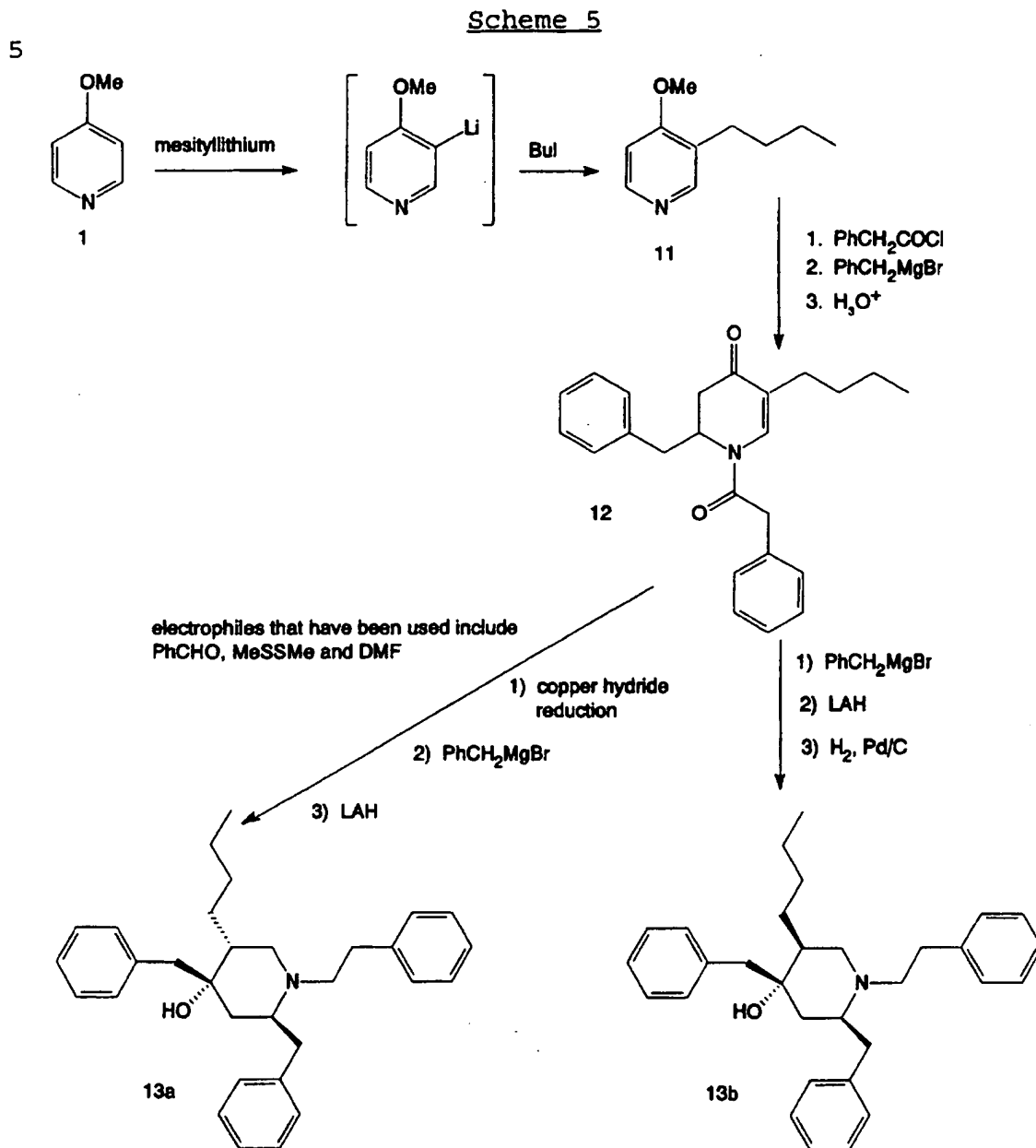
Other variations of this versatile synthetic approach are also possible (See, Scheme 4). Again, the benzyl group was originally introduced as a Grignard reagent so that can be varied (see 2 → 3 above). The cuprate reagent can be varied as well as the final benzyl Grignard reagent. The net result of this chemistry is the preparation of 2,4,4,6-tetrasubstituted N-alkylpiperidines.

10

Scheme 4

15 One can also take advantage of the ortho lithiation of methoxy pyridines described by Comins, D. L., et al.,

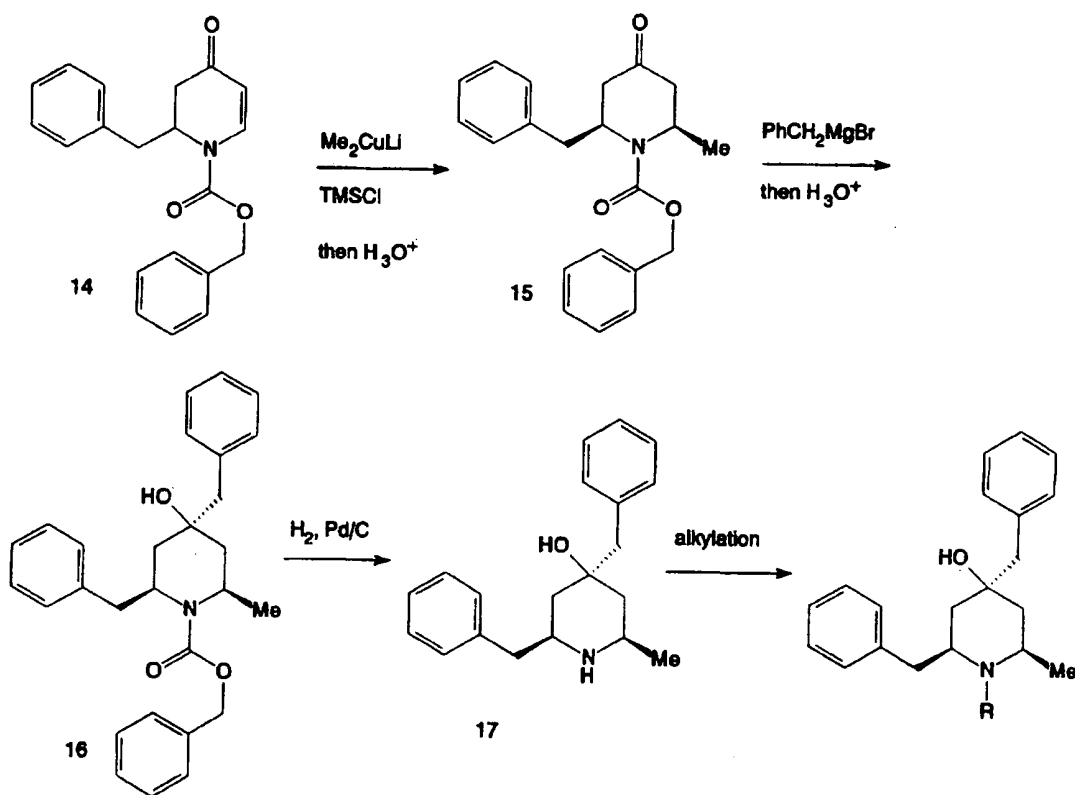
Tetrahedron Lett. 29 (1988). Routes to novel piperidines are illustrated in Scheme 5 below.



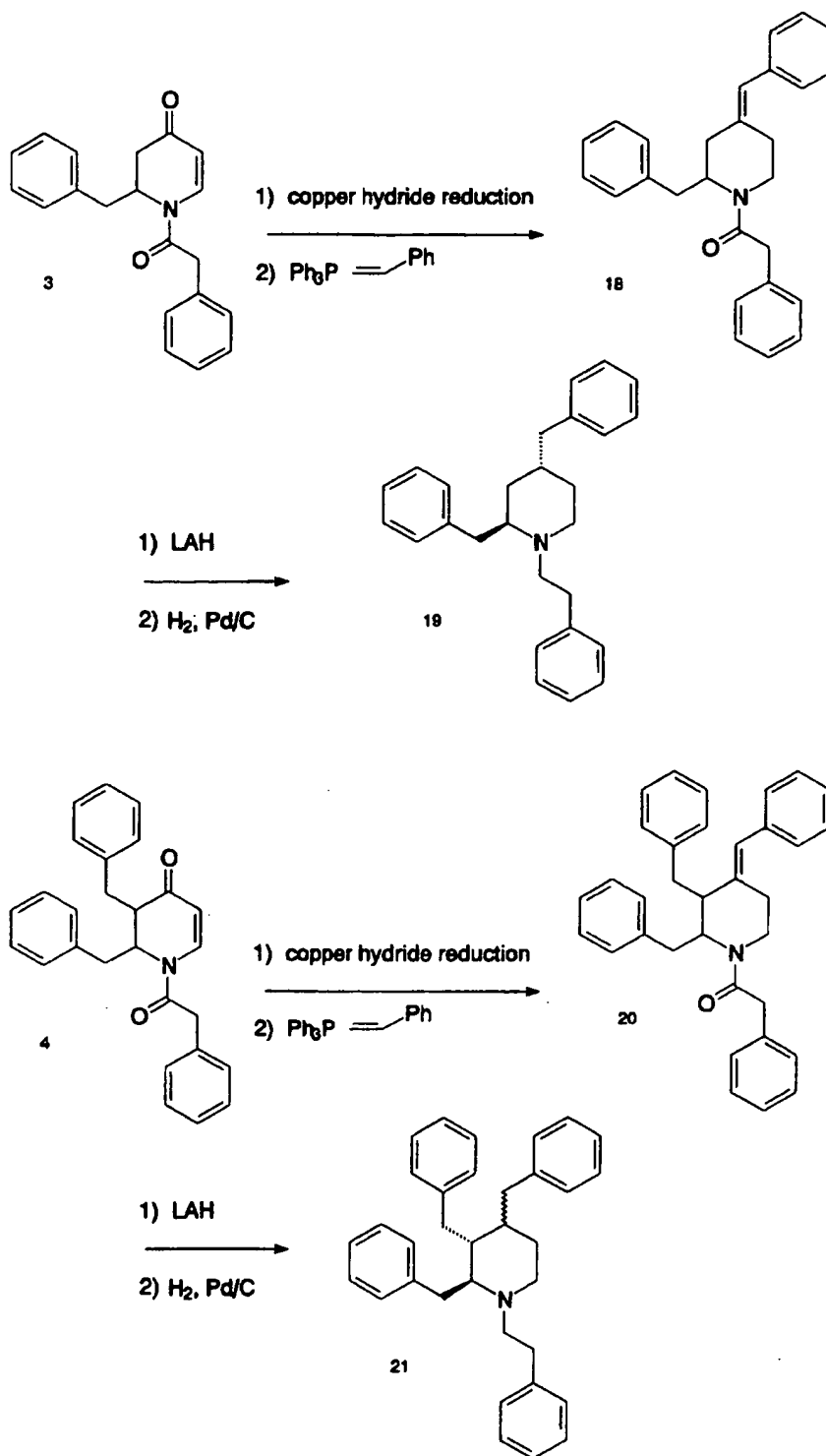
By choosing benzyl chloroformate as the initial
 10 electrophilic N-acylating agent, one can prepare a
 family of piperidines without a substituent on the
 nitrogen atom (Scheme 6). N-Phenoxycarbamates can be
 removed by catalytic hydrogenation with PtO_2 in ethanol
 (see Comins, D.L. et al., *Tet. Lett.* 32:5697 (1991)).

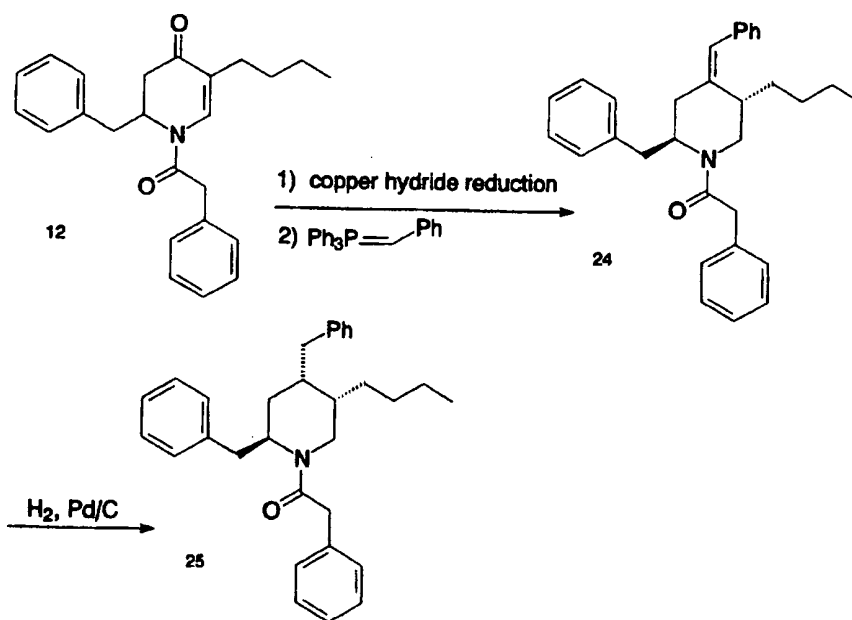
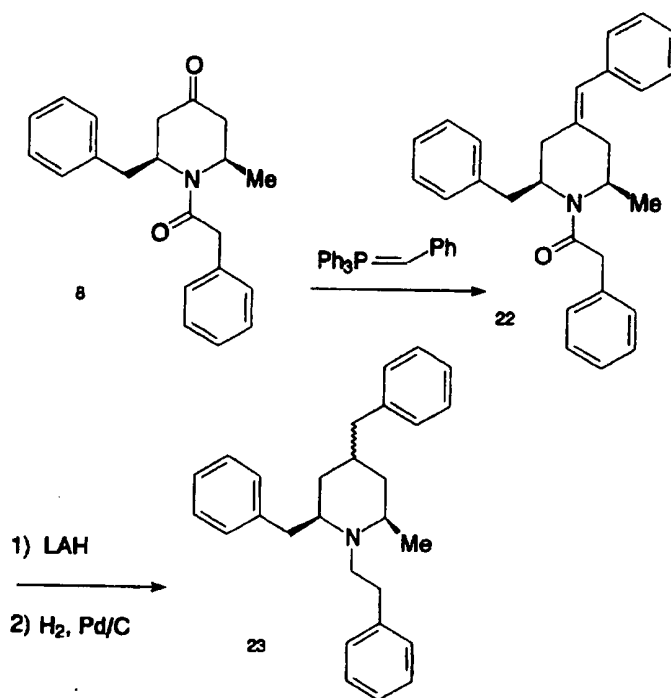
Carbamates formed from other chloroformates can be removed from 2,3-dihydro-4-pyridones by treatment with bases such as sodium methoxide in methanol under reflux. Then, the electrophilic reagents mentioned
 5 above may be used to alkylate these piperidine nitrogens. Also note that a variety of electrophilic reagents can be used so that the final products 13 will contain various substituents at the 5-position.

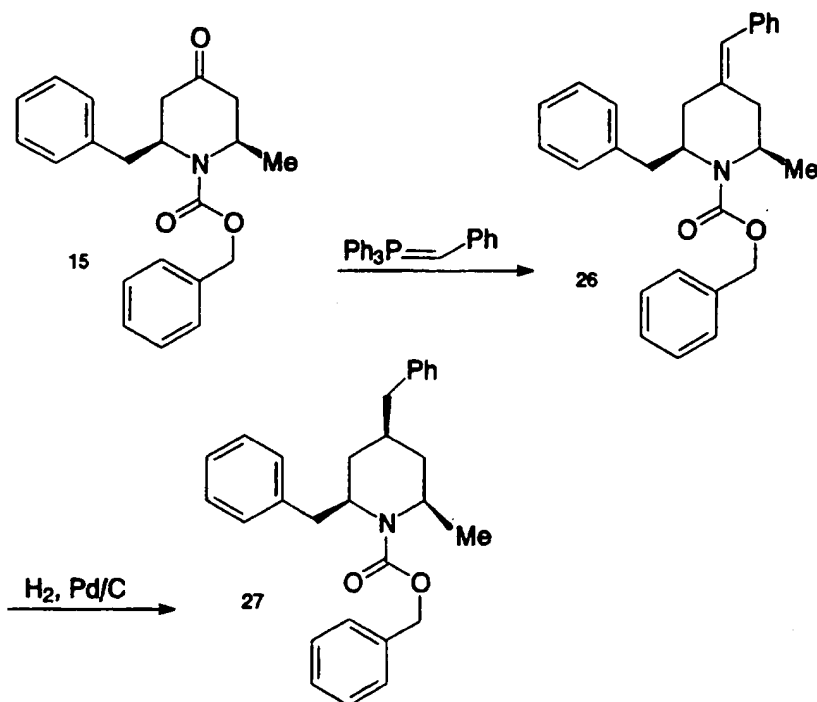
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Scheme 6

15 All of the above combinations can be readily made without the hydroxy substituent at C-4 of the piperidine as shown below via Wittig olefination of the piperidone followed by reduction (Scheme 7).

Scheme 7

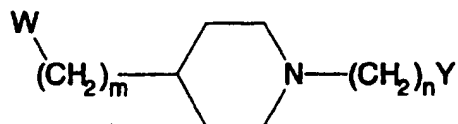




In the transformations of 20 to 21 and 22 to 23,
 stereocontrol of the hydride reductions may be achieved
 5 by substituting other hydride reagents in place of LAH.

See, Comins, D. L., et al., *J. Org. Chem.* 55:2574
 (1990), Comins, D. L., et al., *Tetrahedron Lett.* 29
 (1988), and Comins, D. L., et al., *J. Am. Chem. Soc.*
 10 116:4719 (1994).

An example of compounds having Formula III include
 those having Formula IIIa:



15

wherein

- 40 -

W is an adamantyl group or an optionally substituted aryl group;

Y is CH₃, CN, CO₂R, carboxamido, an optionally substituted cycloalkyl group or an optionally substituted heterocycloalkyl group;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, 3;

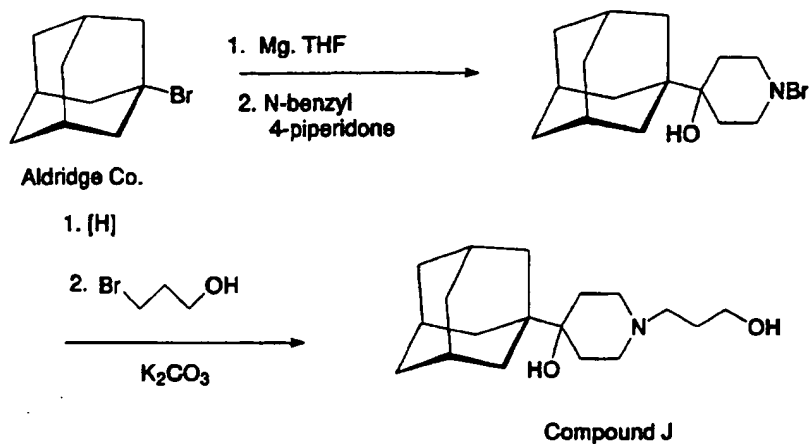
with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAR, COAr, hydroxy, =Y₁, -Y₁, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y₁ is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

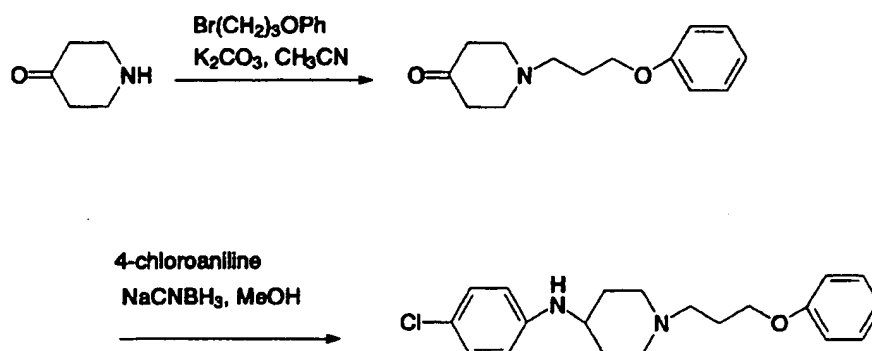
Generally, when Y is an aminoalkyl or guanidinoalkyl, n must be greater than 1.

In general, compounds having Formula III may be prepared by reaction of an appropriately substituted piperidine with one of the electrophilic reagents mentioned above. Where W is an adamantyl group, the compounds may be prepared as shown in Scheme 8.

Preferably, such adamantyl groups are 1-adamantyl.

Scheme 8

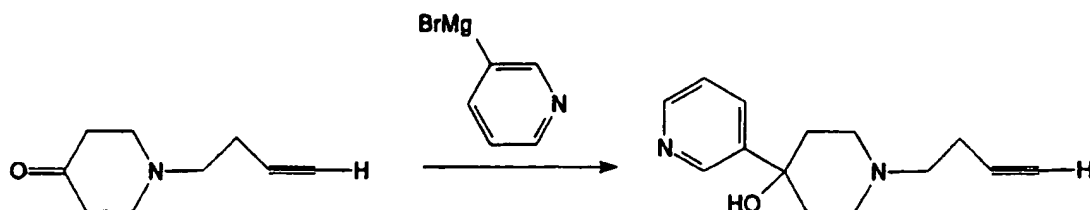
or:



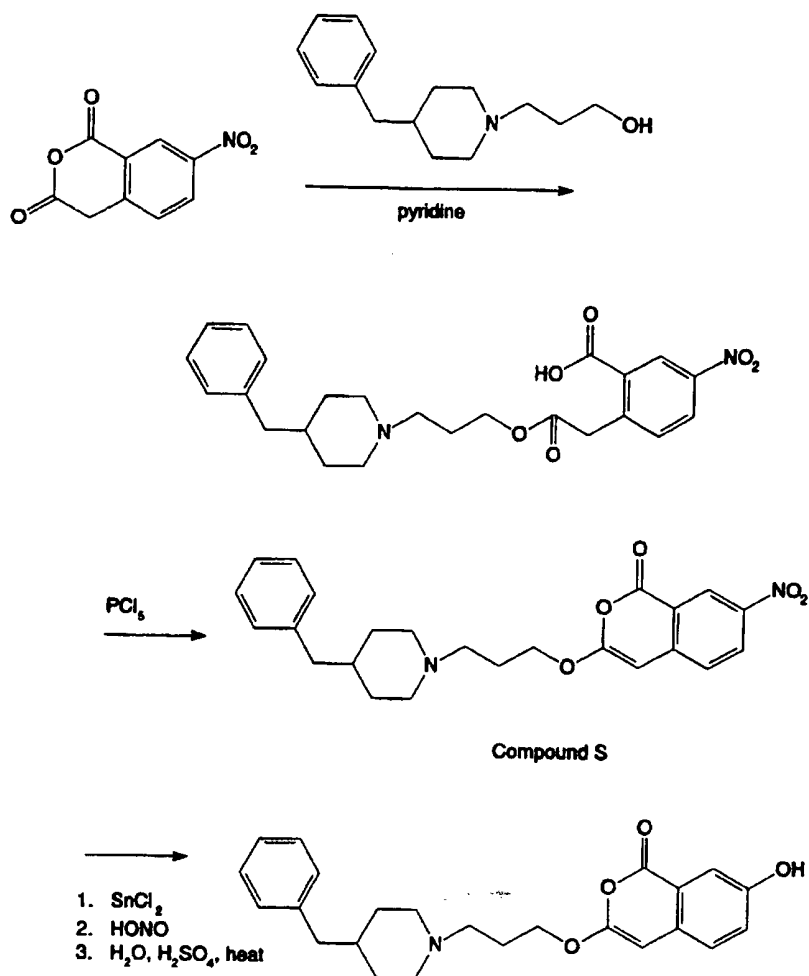
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Where W is a heteroaryl group, the compounds may be prepared using an aryl lithium or grignard reagent as shown in Scheme 9.

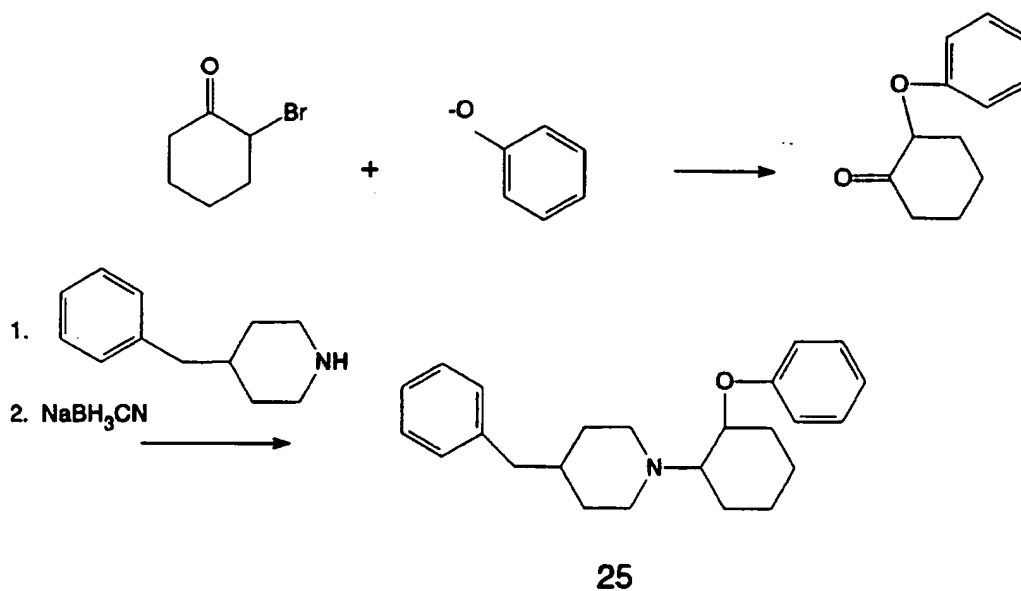
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Scheme 9

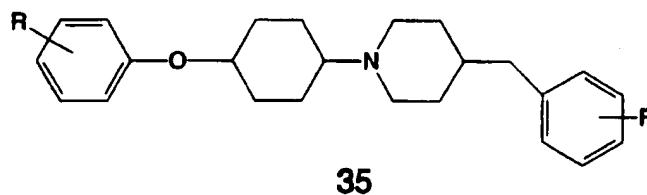
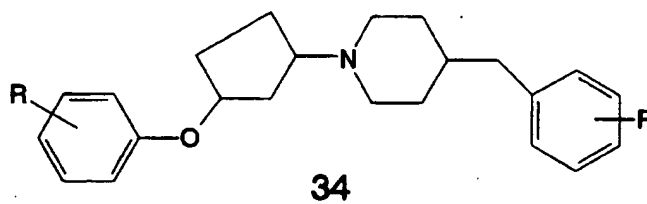
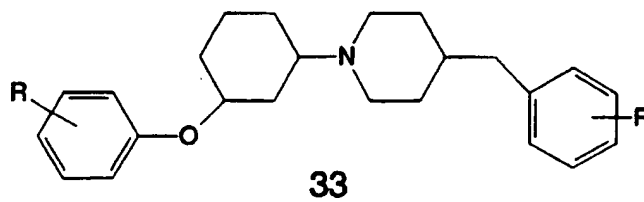
Where Y is a 7-substituted isocoumarin, the compounds may be prepared as set forth in Scheme 10.

Scheme 10

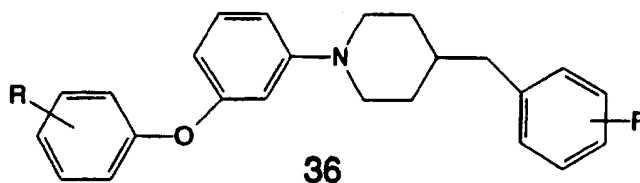
- 5 See, Kerrigan et al., *J. Med. Chem.* 38:544 (1995) for methods of making such 7-substituted isocoumarins wherein the 7-substituent may be an amino group, a nitro group, or amido group.
- 10 Where Y is an optionally substituted cycloalkyl group or optionally substituted heterocycloalkyl group, and r, s and t are 0, the compounds may be prepared as shown in Scheme 11.

Scheme 11

5 Other cyclized analogs include compounds such as 33-36.

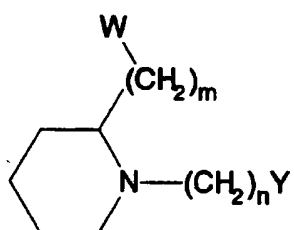


- 44 -



Another example of compounds within the scope of

5 Formula *III* includes compounds having the Formula *IIIb*:



10 wherein

W is an adamantyl group or an optionally substituted aryl group;

15 Y is CH₃, CN, CO₂R, carboxamido, an optionally substituted cycloalkyl group or an optionally substituted heterocycloalkyl group;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a
20 ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, or 3;

25

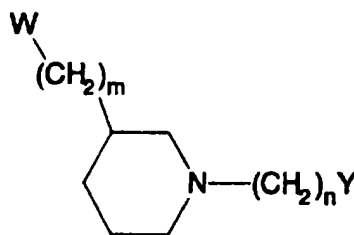
with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAr, COAr, hydroxy, =Y₁, -Y₁, a heterocyclic group, a heteroaryl group, a cycloalkyl

- 45 -

group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y₁ is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the Formula
10 **IIIc**:



15 wherein

W is an adamantyl group or an optionally substituted aryl group;

20 Y is CH_3 , CN , CO_2R , carboxamido, an optionally substituted cycloalkyl group, an optionally substituted heterocycloalkyl group, optionally substituted aryl, optionally substituted aryloxy, SAr , $COAr$, hydroxy, $=Y_1$, $=Y_1$, a heterocyclic group, a heteroaryl group, an
25 amino group, an amido group, a ureidoalkyl group, a guanidinoalkyl group, or $O-N=CR_1R_2$, where R_1 and R_2 are independently aryl or lower alkyl;

R is alkyl, an aminoalkyl group, an amidoalkyl group, a
30 ureidoalkyl group, or a guanidinoalkyl group;

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted

- 46 -

aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

5

m is 0, 1, 2, or 3;

with the proviso, that when W is adamantyl, then Y may also be optionally substituted aryl, optionally substituted aryloxy, SAR, COAr, hydroxy, $\equiv Y_1$, $=Y_1$, a

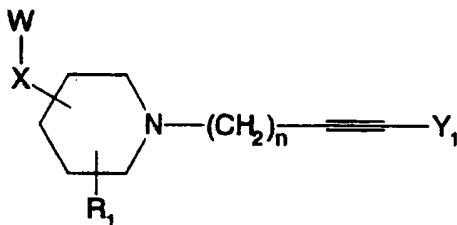
10 heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; wherein

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally

15 substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the Formula

20 **IIId**:



25 wherein

W is an adamantyl group or an optionally substituted aryl group;

30 X is a bond, $(CH_2)_m$, oxygen, or NR;

- 47 -

Y_1 is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

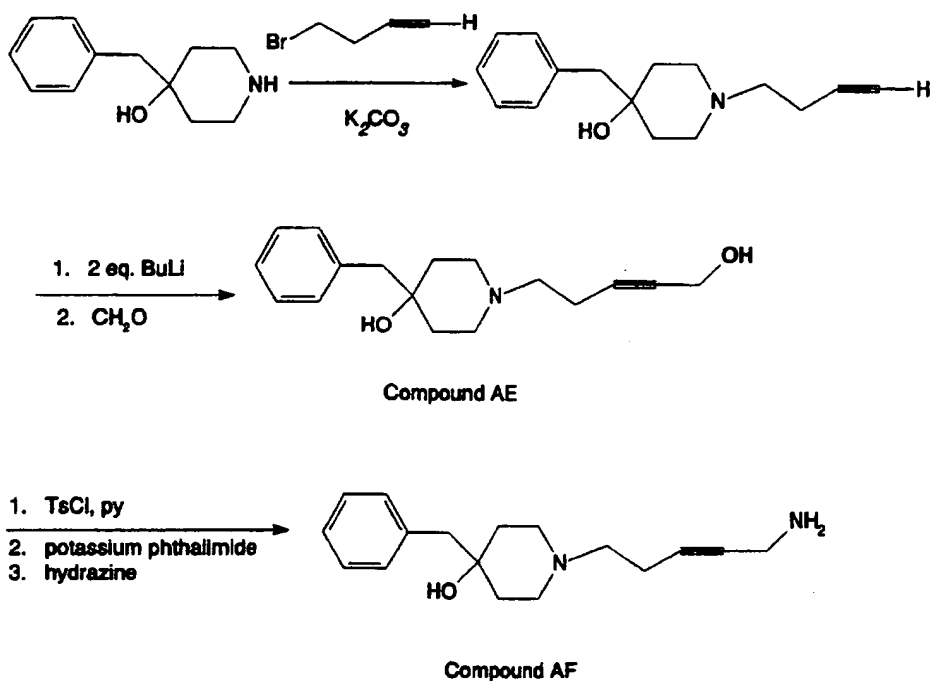
- 5 R_1 is hydrogen, hydroxy, halo, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a
10 heteroaryl substituted alkyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 0, 1, 2, or 3;

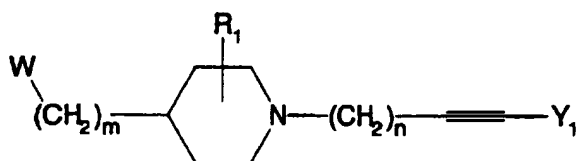
- 15 with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

- Where the compounds having Formula **IIId** terminate with
20 an alkyne (Y_1 = hydrogen), a propargylalcohol (Y = hydroxyalkyl), or propargylamine (Y_1 = aminoalkyl) residue, they may be prepared according to Scheme 12.

Scheme 12

5

Another example includes compounds having the
Formula **IIIe**:



10

wherein

W is an adamantyl group or an optionally substituted
15 aryl group;

Y₁ is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl
group, an amidoalkyl group, a ureidoalkyl group, or a
guanidinoalkyl group;

20

- 49 -

R_1 is hydrogen, hydroxy, halo, alkylcarboxy, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxyalkyl, optionally substituted benzyloxyalkyl, a heterocyclic group, a heterocyclic substituted alkyl group, heteroaryl, or a heteroaryl substituted alkyl group;

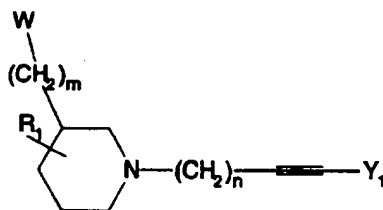
n is 0, 1, 2, 3, 4, 5, or 6; and

10 m is 0, 1, 2, or 3;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

15

Another example includes compounds having the Formula **IIIIf**:



20

wherein

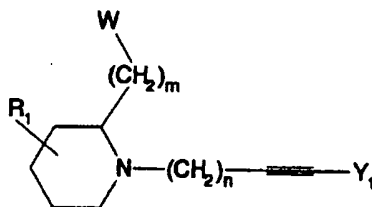
25 W , Y_1 , R_1 , n and m are the same as described in Formula **IIIIf**;

with the proviso that when W is an adamantyl group, then Y_1 may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

30

Another example includes compounds having the Formula **IIIIf**:

- 50 -



wherein

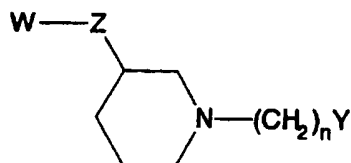
5

W, Y₁, R₁, n and m are the same as described in Formula IIIe;

with the proviso that when W is an adamantyl group,
 10 then Y₁ may further be an optionally substituted aralkyl group, or an optionally substituted aryl group.

Another example includes compounds having the
 Formula IIIh:

15



wherein

20

W is an adamantyl group or an optionally substituted aryl group;

Y is optionally substituted aryl, optionally
 25 substituted aryloxy, SAR, COAr, hydroxy, =Y₁, -Y₁, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

- 51 -

Y_1 is hydrogen, alkyl, hydroxyalkyl, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

5 Z is $(CH_2)_m$, oxygen, sulfur, or NR ;

m is 0, 1, 2, or 3; and

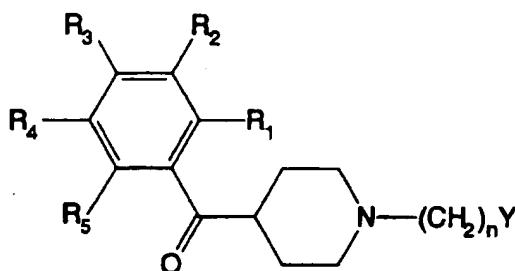
n is 1, 2, 3, 4, 5, or 6.

10

Examples of compounds having Formula *IIIh* include 3-benzyl-1-(3-phenoxypropyl)piperidine, 3-benzyl-1-(2-phenoxyethyl)piperidine, 3-benzyl-1-(2-phenethyl)piperidine, 3-benzyl-1-[2-(3-trifluoromethyl)phenethyl]piperidine, 3-benzyl-1-[2-(4-aminophenyl)ethyl]piperidine, 3-benzyl-1-[2-(4-chlorophenyl)-ethyl]piperidine, 3-benzyl-1-[2-(4-fluorophenyl)ethyl]piperidine, and 3-benzyl-1-[2-(4-methoxyphenyl)ethyl]piperidine.

20

Another example includes compounds having the Formula (*IIIi*):



25

wherein

R_1 - R_5 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, a heterocyclic group, a heteroaryl group, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, hydroxyalkyl, nitro, amino, cyano,

30

- 52 -

acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, or alkylthiol;

n is 1, 2, 3, 4, 5, or 6;

5

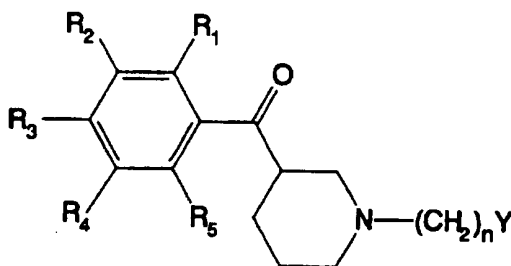
Y is optionally substituted aryl, optionally substituted aryloxy, SAR, COAr, hydrogen, hydroxy, $\equiv Y_1$, $\equiv Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group.

Compounds having Formula *IIIIi* may be prepared by reaction of the 4-benzoylpiperidine with one of the electrophiles listed above.

20

Another example includes compounds having Formula (*IIIIj*):



25

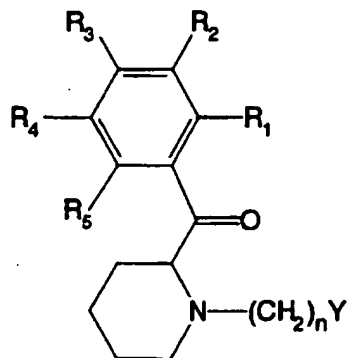
wherein

R₁-R₅, n, Y and Y₁ are the same as described for formula *IIIIi*.

30

Another example includes compounds having the Formula (*IIIIk*):

- 53 -



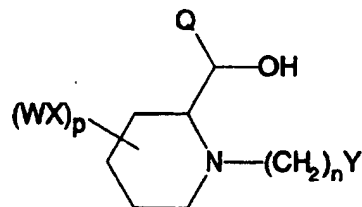
wherein

5

R₁-R₅, n, Y and Y₁ are the same as described in formula IIIi.

Another example includes compounds having the

10 Formula (IIII):



15 wherein

W is optionally substituted aryl;

Y is optionally substituted aryl, optionally substituted aryloxy, an optionally substituted aryloxy group, SAr, COAr, hydrogen, hydroxy, =Y₁, =Y₁, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

25

Y₁ is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted

- 54 -

aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

Q is hydrogen, alkyl, aryl, aralkyl, a heterocyclic group, a heterocyclic substituted alkyl group, an aryl group, or an aralkyl group;

X is a bond, $(CH_2)_m$, oxygen, or sulfur;

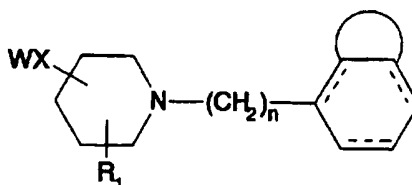
10 m is 0, 1, 2, or 3;

n is 1, 2, 3, 4, 5, or 6; and

p is 0 or 1.

15

Another example includes compounds having the Formula (III m):



20 wherein

W is optionally substituted aryl;

25 X is a bond, $(CH_2)_m$, oxygen, sulfur, or NR;

R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;

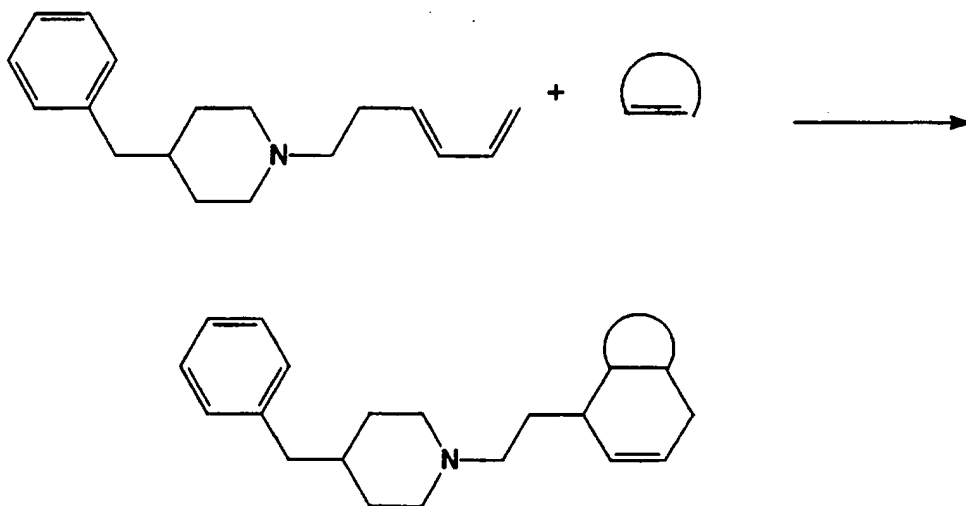
30 R₁ is hydrogen, hydroxy, aryl, or aralkyl;

n is 1, 2, 3, 4, 5, or 6;

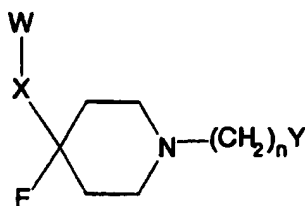
— = single or double bond; and

□ = carbon ring or heterocyclic ring, with the proviso that said carbon ring is not part of a naphthyl group.

Compounds having Formula *IIIm* may be prepared by a
5 Diels-Alder reaction as shown below:



Another example includes compounds having the
10 Formula (*IIIn*):



wherein

15

W is an adamantyl group or an optionally substituted aryl group;

X is a bond or (CH₂)_m;

20

Y is CH₃, CN, CO₂R; an optionally substituted aryl group, an optionally substituted aryloxy group, SAr,

- 56 -

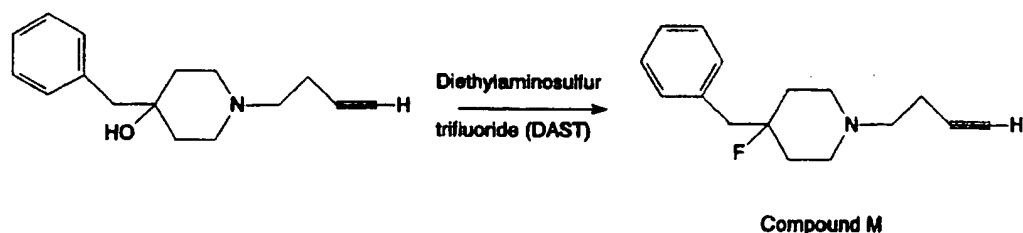
COAr, hydroxy, $\equiv Y_1$, $\Rightarrow Y_1$, a heterocyclic group, a heteroaryl group, a cycloalkyl group, an amino group, an amido group, a ureido group, or a guanidino group;

- 5 Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally substituted aralkyl group, an optionally substituted aryl group, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group
- 10 R is alkyl, hydroxy, an aminoalkyl group, an amidoalkyl group, a ureidoalkyl group, or a guanidinoalkyl group;
- n is 0, 1, 2, 3, 4, 5, or 6; and
- 15 m is 0, 1, 2, or 3.

Compounds having Formula **IIIIn**, where the group R_1 is fluoro, may be prepared by reaction of the corresponding hydroxy piperidine with

- 20 diethylaminosulfur trifluoride as shown in Scheme 13.

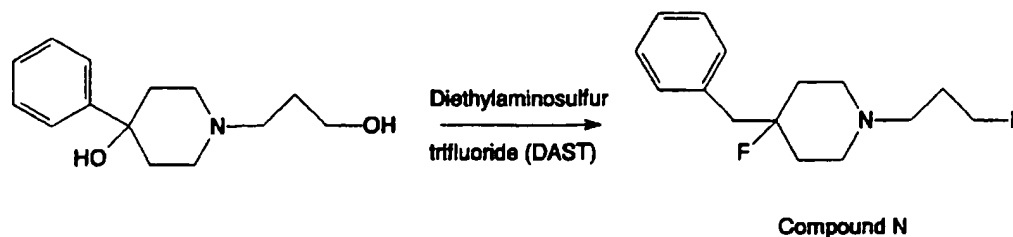
Scheme 13



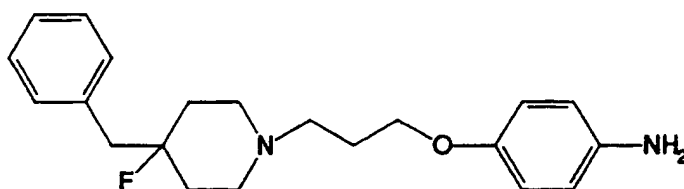
25

See, Sharma, R.A.; Korytnyk, W.; *Tetrahedron Lett* 573 (1977); and Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* 6:183 (1977).

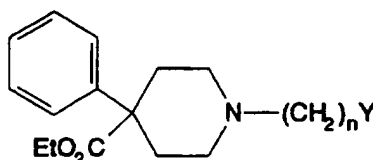
- 57 -



5 An example of compounds having Formula *IIIIn* includes:



10 Another example includes compounds having the
Formula (*IIIIo*):



15 wherein

Y is hydrogen, hydroxy, CH₃, CN, CO₂R, optionally
substituted aryl, optionally substituted aryloxy,
20 optionally substituted arylthioxy, optionally
substituted aroyl, =Y₁, =Y₁, optionally substituted
heterocyclic group, optionally substituted
heterocycloxy, optionally substituted heteroaryl,
optionally substituted heteroaryloxy, optionally
25 substituted cycloalkyl group, optionally substituted
cycloalkoxy group, amino, amido, ureido, or guanidino;

Y_1 is hydrogen, alkyl, hydroxyalkyl, optionally substituted aralkyl, an optionally substituted aryl, aminoalkyl, amidoalkyl, ureidoalkyl, or guanidinoalkyl; and

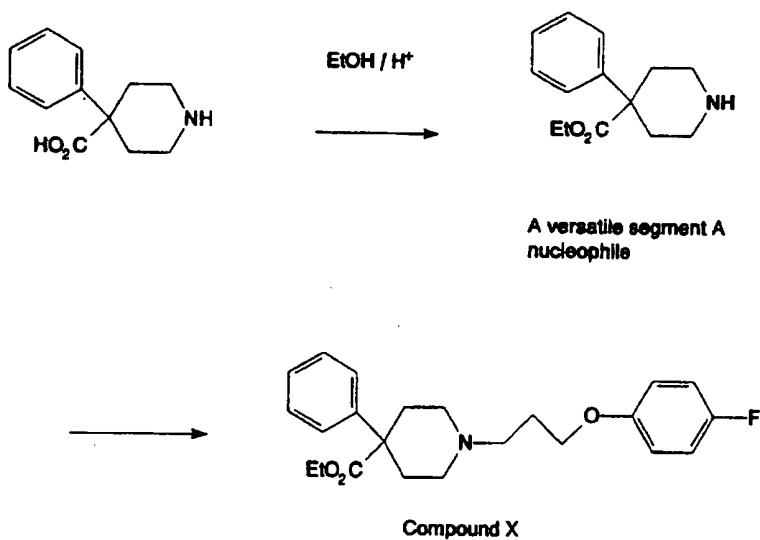
5

n is 0, 1, 2, 3, 4, 5 or 6.

Compounds having Formula *III*o may be prepared according to Scheme 14.

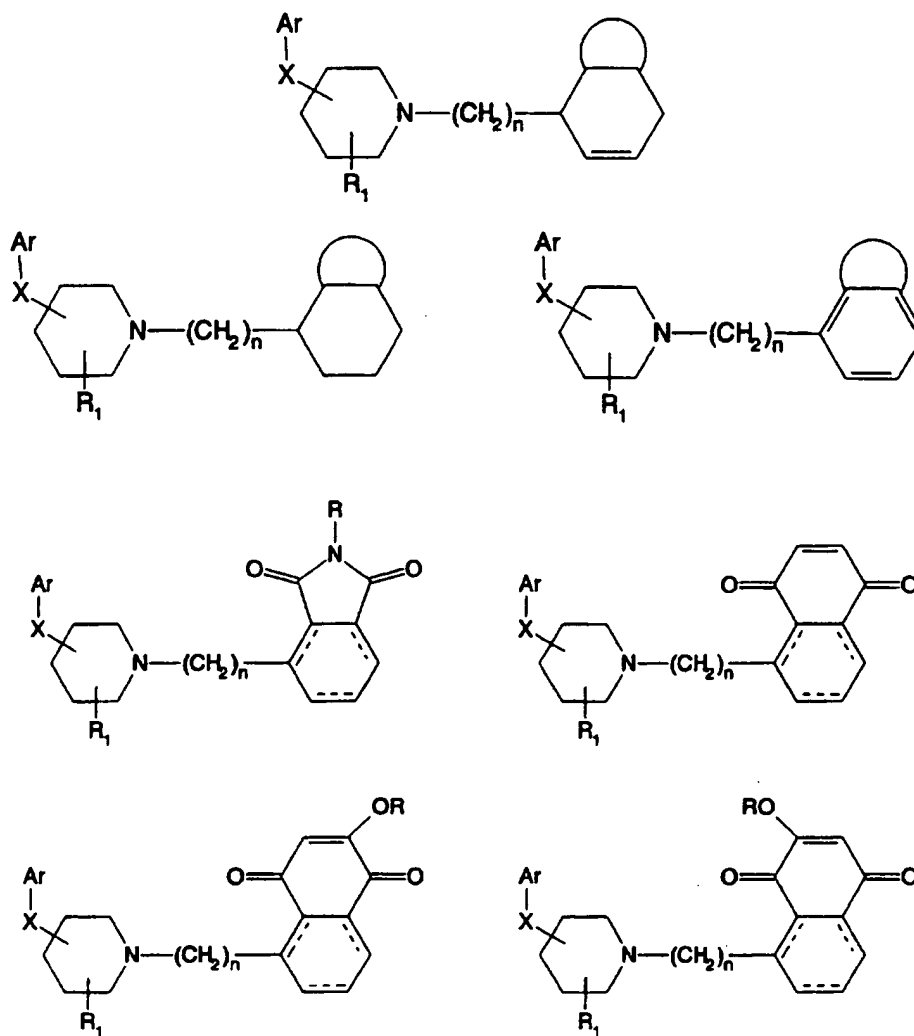
10

Scheme 14

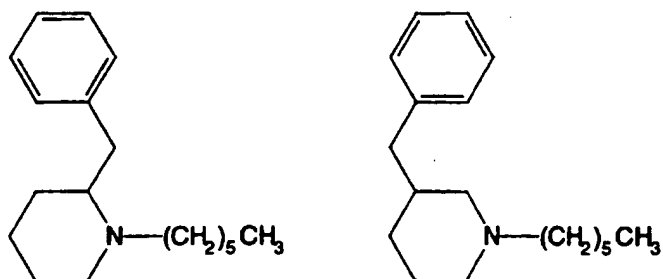


15

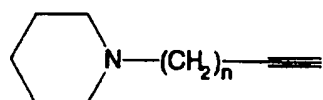
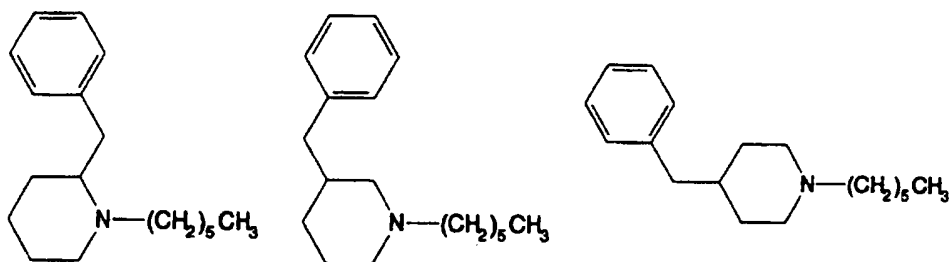
Particular examples of compounds having Formula *III* include:



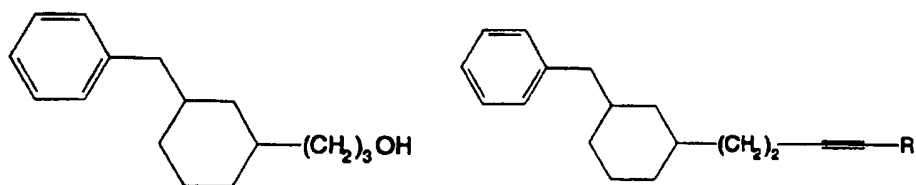
5 wherein n is 0, 1, 2, 3, 4, 5 or 6;



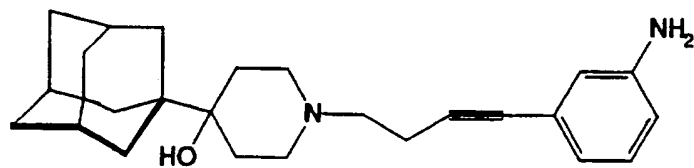
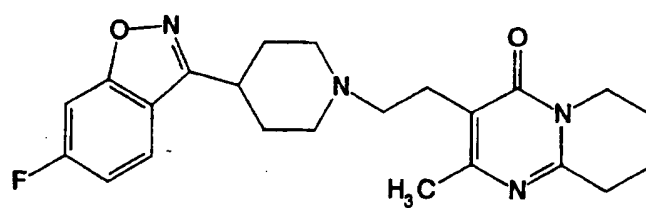
- 60 -



5

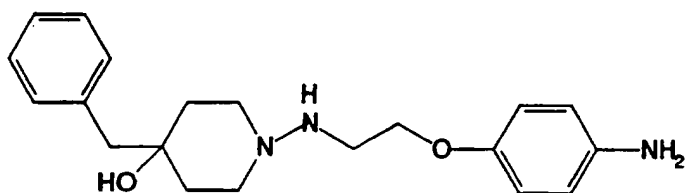
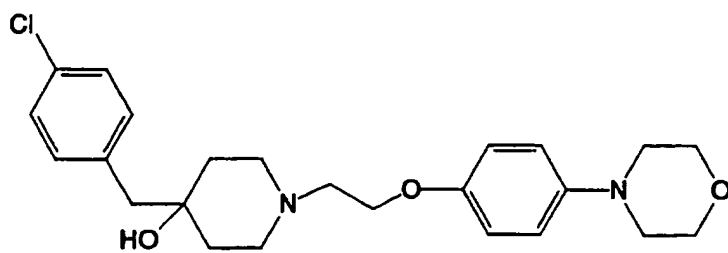
 $n = 1, 2;$  $R = \text{hydrogen, aryl};$

10

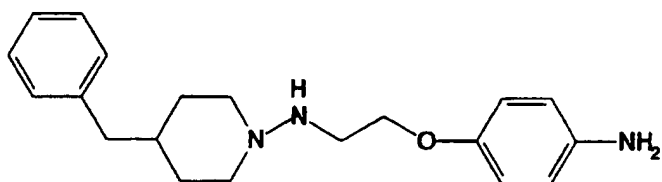


15

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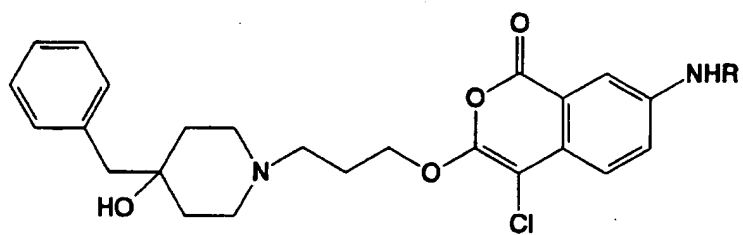


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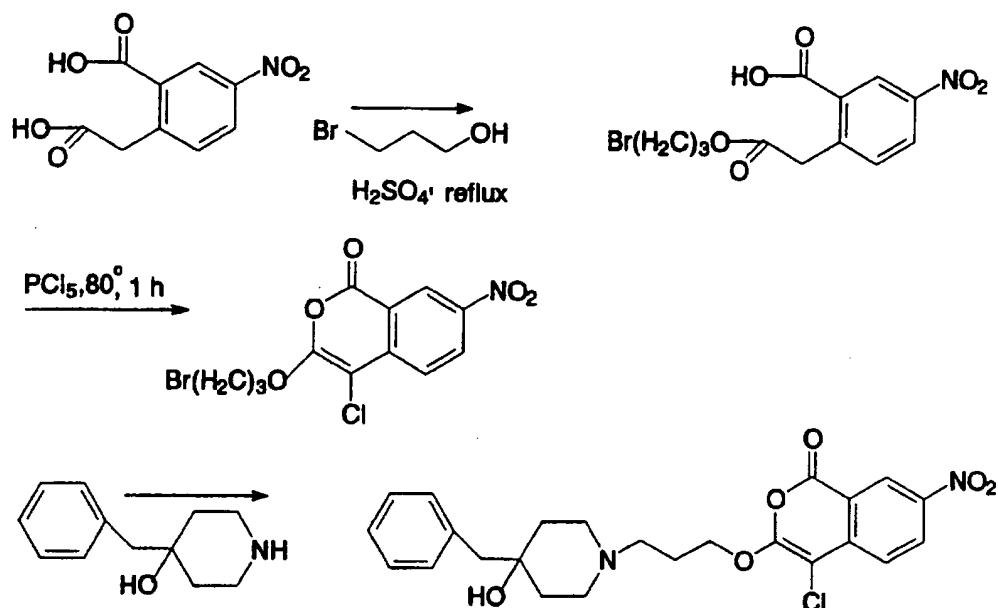


and

10



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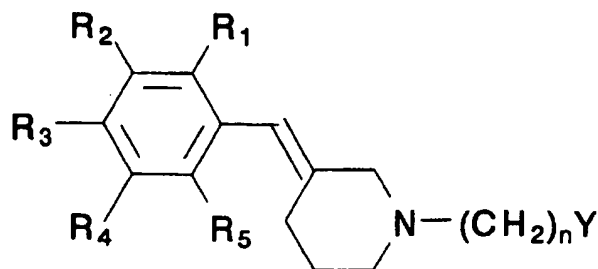
Scheme 15

5

Method of Harper and Powers, *Biochemistry* 24:7200-7213 (1985).

Additional compounds having Formula *III* include 4-
 10 benzyl-1-(3-hydroxy-1-methylpropyl)piperidine, 4-
 benzyl-1-(2-hydroxyethyl)piperidine, 1-benzyl-3-
 hydroxy-3-phenylpiperidine, 3-hydroxy-3-phenyl-1-
 phenethylpiperidine, 3-hydroxy-3-phenyl-1-
 (phenylpropyl)piperidine, and 4-benzoyl-1-(3-
 15 hydroxypropyl)piperidine.

Examples of compounds having Formula *IV* include those having the Formula (*IVa*):



20

wherein

R_1 - R_5 are independently hydrogen, halo, haloalkyl, aryl,
 5 fused aryl, a heterocyclic group, a heteroaryl group,
 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl,
 arylalkynyl, hydroxyalkyl, nitro, amino, cyano,
 acylamido, hydroxy, thiol, acyloxy, azido, alkoxy,
 carboxy, carbonylamido, or alkylthiol;

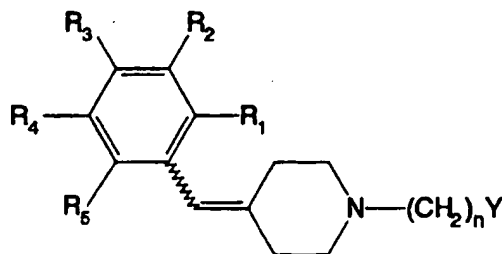
10

n is 1, 2, 3, 4, 5, or 6;

Y is optionally substituted aryl, optionally
 substituted aryloxy, SAr , $COAr$, hydrogen, hydroxy, $\equiv Y_1$,
 15 $\equiv Y_1$, a heterocyclic group, a heteroaryl group, a
 cycloalkyl group, an amino group, an amido group, a
 ureido group, or a guanidino group; and

Y_1 is hydrogen, alkyl, hydroxyalkyl, an optionally
 20 substituted aralkyl group, an optionally substituted
 aryl group, an aminoalkyl group, an amidoalkyl group, a
 ureidoalkyl group, or a guanidinoalkyl group.

Another example includes compounds having the
 25 Formula (IVb):



30 wherein

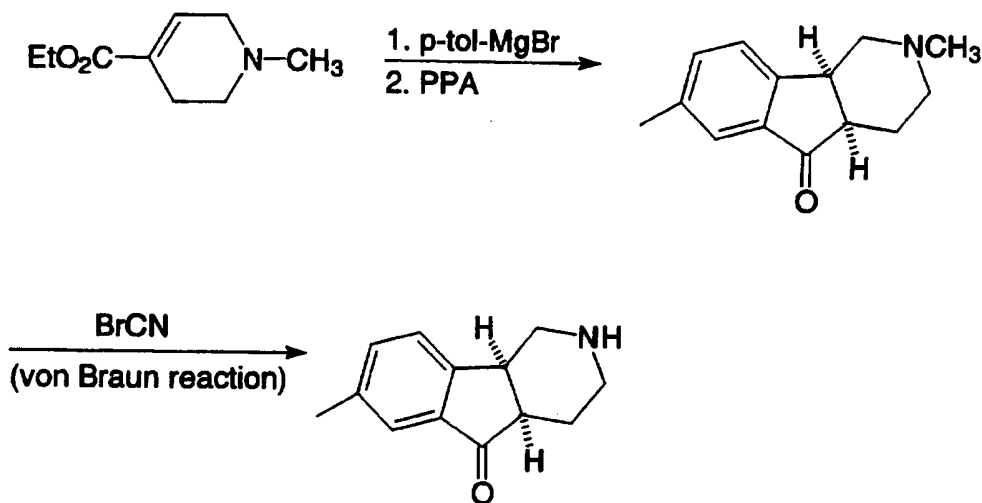
R_1 - R_5 , n , Y and Y_1 are the same described in formula
 IVa.

Compounds having Formula IV may be prepared by reaction of the corresponding piperidone with a Wittig reagent derived from a benzyl bromide. Alternatively, a benzyl grignard reagent may be reacted with the piperidone to give the hydroxybenzyl piperidine which may be dehydrated with sulfuric acid and heat.

Particular examples of compounds having Formula IV include 1-benzyl-4-(m-fluorobenzylidene)piperidine, 1-(3-hydroxypropyl)-4-benzylidenepiperidine, and 1-hexyl-4-benzylidenepiperidine.

Compounds having Formula V may be prepared according to Scheme 16 followed by reaction with one of the electrophiles mentioned above.

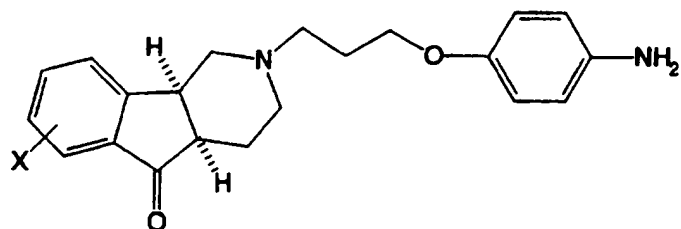
Scheme 16



20

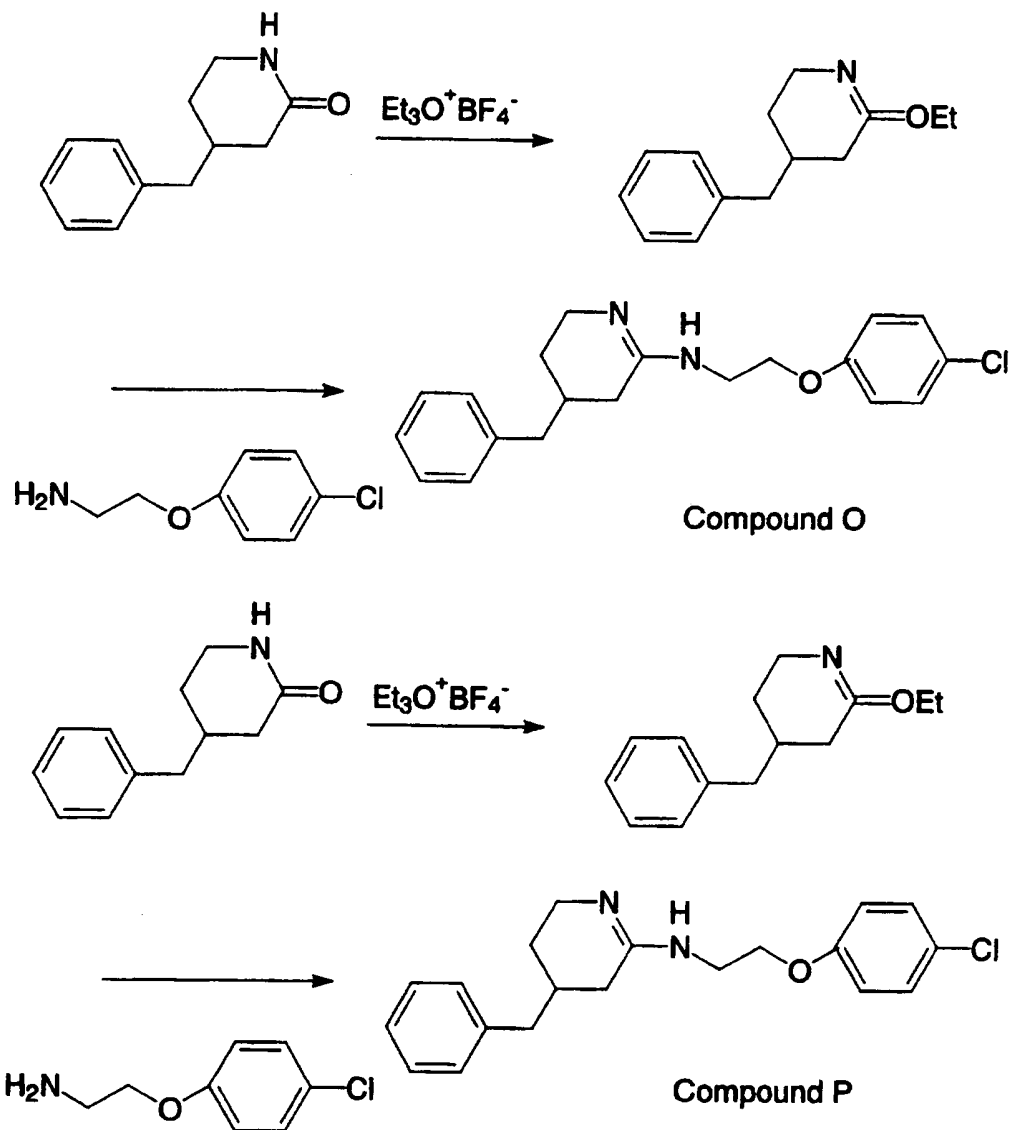
See, Cook et al., *J. Med. Chem.* 38:754 (1995).

An example of compounds having Formula V include:



Compounds having Formula VI may be prepared according
5 to Scheme 17.

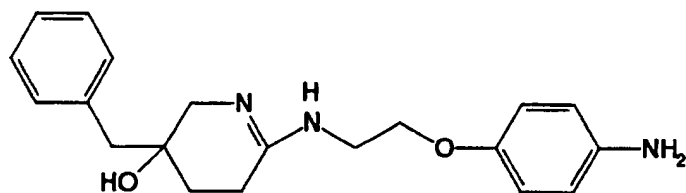
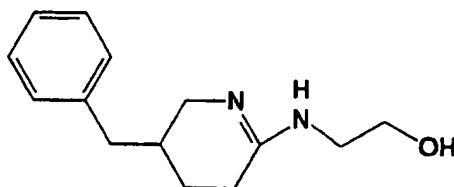
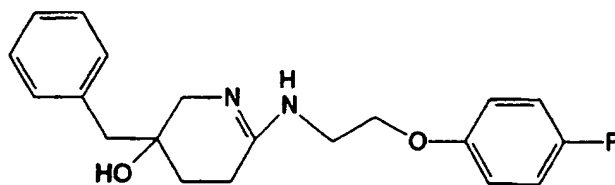
Scheme 17



5

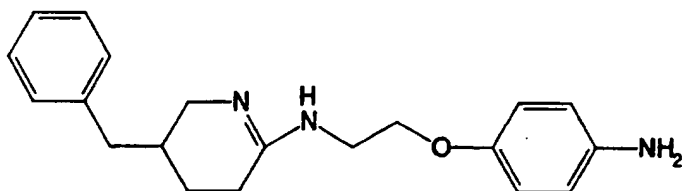
By varying the choice of the amine nucleophile, one can synthesize a family of amidines including the following:

- 67 -



5

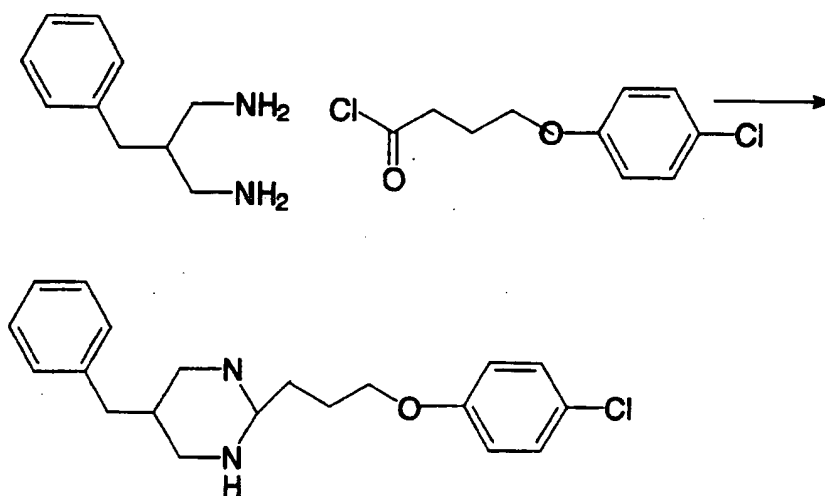
and



10

Compounds having Formula VII may be prepared according to Scheme 18.

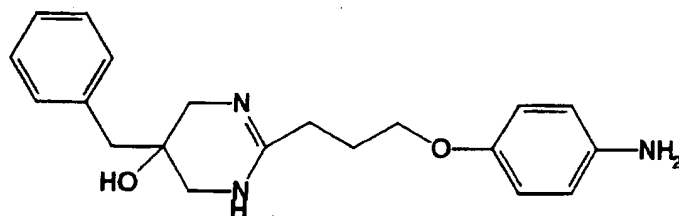
15

Scheme 18

Compound Q

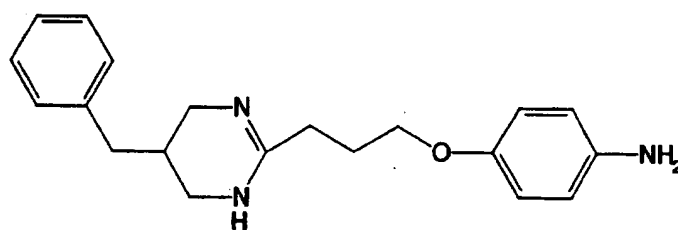
5

Examples of compounds having Formula VII include:



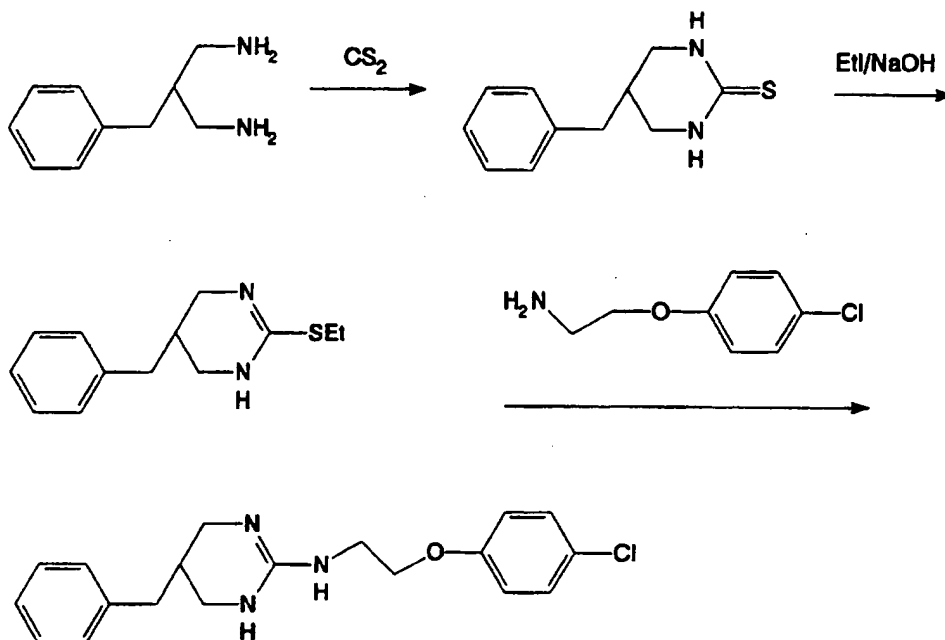
10

and



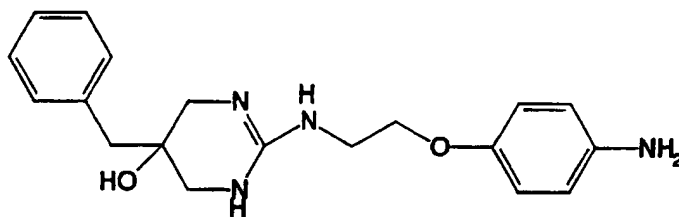
15

Compounds having Formula VIII may be prepared according to Scheme 19.

Scheme 19

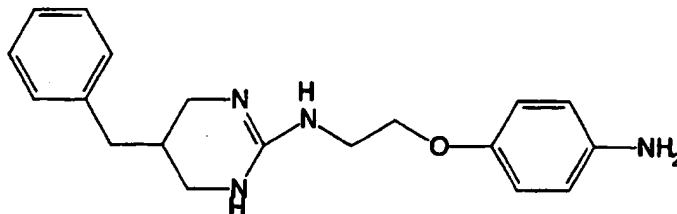
5

Examples of compounds having Formula VIII include:

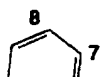


10

and



15 Compounds having Formula IX may be prepared according to Scheme 20.

Scheme 20

ERROR: ioerror
OFFENDING COMMAND: image

OPERAND STACK:
--nostringval--
--nostringval--
--nostringval--
--nostringval--
--nostringval--
--nostringval--

